CIGARETTE SMOKING AND
CORONARY HEART DISEASE

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CIGARETTE SMOKING AND CORONARY HEART DISEASE

(Fourth in a Series of Reports Prepared for
The Council for Tobacco Research)

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PART ONE

INTRODUCTION AND SUMMARY

This is the fourth and last review that the author has prepared for the Council for Tobacco Research. The major concern in this article is to examine the relationship between cigarette smoking and coronary disease. There is some overlapping with the three previous articles. Carbon monoxide, which was the subject of the first riview, is again discussed because it has recently been implicated in the causation of atherosclerosis. Nicotine, which was included in the review on passive smoking, is elaborated upon in the present article because its known pharmacologic effects can be potentially harmful to a patient with angina pectoris. The epidemiologic investigation relating to respiratory disease is again scrutinized, this time as it relates to the mortality of coronary heart disease, particularly of myocardial infarction. There is one special feature introduced in this report, which is a page by page critique of the US Public Health publications on "Smoking and Health." The seven monographs appearing between 1964 and 1973 include a total number of 753 references. These have been examined to determine the scientific basis of the theory that smoking causes coronary heart disease, as implied in the US Public Health publications.

The author has also examined the literature on three disease entities included under the term coronary heart disease, namely, angina pectoris, myocardial infarction and coronary atherosclerosis. There are 1169

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articles which report investigations on the effects of smoking as determined by mortality and morbidity statistics, antemortem and postmortem examination of patients, and experiments performed on healthy subjects and animals. A special effort has been made to separate the various forms of research. The sections appearing under Part Two contain information relating to patients with angina pectoris, myocardial infarction or coronary atherosclerosis; the sections under Part Three are devoted entirely to mortality statistics; the sections under Part Four also contain epidemiologic studies, with emphasis on the differences in morbidity among smokers as compared with nonsmokers; and finally the sections under Part Five deal with the acute effects of smoking in humans and the acute and chronic effects of experimental exposure to cigarette smoke in animals. In each section there are Additional Bibliographic Lists of 761 articles which discuss coronary heart disease, epidemiologic investigation and cardiovascular pharmacology in general terms.

It should be stated at the outset that the conclusions arrived at by the author are different from the statements which appear in the US Public Health publications. There is still no definitive evidence that smoking is the most important cause of coronary heart disease, although almost all review articles, editorials and miscellaneous papers accept the conclusions appearing in the US Public Health publications. The total number of secondary publications is 329 and they are listed under Part Six.

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On the basis of examination of 2,259 articles (original, additional and secondary bibliographies) the author has made the following interpretations of the present state of knowledge relating to cigarette smoking and coronary heart disease:

I. Angina Pectoris. Angina can be initiated by smoking, and the disease has been referred to as tobacco angina. The incidence is 6% of all cases of angina pectoris, and 1% of angina pectoris patients who are smokers. The majority (94%) of patients suffer from effort angina and in these smoking does not precipitate symptoms and signs of myocardial ischemia.

II. Myocardial Infarction. Myocardial infarction is a more serious disease than angina pectoris. In retrospective studies, the incidence of nonsmokers among patients with myocardial infarction is 18%, whereas in the control group it is 33%. That myocardial infarction can occur in nonsmokers suggests the importance of risk factors other than cigarette smoking. Although smoking is prevalent in patients, it does not influence the prognosis. The duration of survival, the severity of infarction and the appearance of complications are not different for smokers and nonsmokers.

III. Atherosclerosis. The clinical manifestations of atherosclerosis include coronary heart disease, stroke and intermittent claudication. Postmortem examination and retrospective and prospective studies indicate a prevalence of smokers among patients suffering from these diseases. However, a cause and effect relationship cannot be established because of other operative risk factors, such as hypertension and hypercholesterolemia.

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IV. Mortality and Morbidity Statistics in the United States. The most widely quoted reason for the belief that cigarette smoking causes coronary heart disease is the fact that the morbidity and mortality rates are higher for smokers than for nonsmokers. It is unfortunate that most prospective studies have pooled angina pectoris and myocardial infarction as a single disease entity. When the two diseases are separated, there is no association between cigarette smoking and the incidence of angina pectoris.

V. Informative Prospective Studies in Foreign Countries. By the selection of one occupation, i.e., British medical practice, it has been possible to define the relationship of smoking and mortality from coronary heart disease. The mortality ratio of smokers to nonsmokers is 1:23 instead of the higher ratios reported in surveys that include various occupational groups. In the Swedish twin registry, the association of coronary heart disease and smoking is attributed to a genetic predisposition. International comparisons of statistics indicate the importance of blood pressure and the level of cholesterol in the blood in influencing the incidence of coronary heart disease among smokers.

VI. Fixed Risk Factors. The incidence of coronary heart disease is determined by age, sex, and genetic and psychogenic factors. The importance of these factors relative to cigarette smoking has not been determined.

VII. Preventable Risk Factors. Physical inactivity, obesity, diabetes mellitus, diet and socioeconomic factors can increase the predisposition of the individual to coronary heart disease. Although these

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factors may be reduced or prevented, it has not been possible to define their importance relative to cigarette smoking in causation of the disease.

VIII. Preventable Risk Factors Probably Influenced by Smoking. During the evolution of the thesis that cigarette smoking causes coronary heart disease, the following risk factors were claimed to be exaggerated by smoking: electrocardiographic signs of ischemia, hypertension, hypercholesterolemia, hypercoagulability of the blood and reduced availability of oxygen. A comparison between smokers and nonsmokers does not afford a consistent proof that smoking enhances these risk factors. Each of the five factors has a set of independent causes which are more definite than cigarette smoking.

IX. Acute Circulatory Effects of Smoking. To prove that smoking causes coronary heart disease, it is necessary to be able to reproduce the disease in the laboratory. So far, this has not been possible in animals whose condition is documented by pathological examination and studies of heart function. Acute exposure has been performed largely on animals and humans without heart disease, so that it is difficult to relate the results to the disease state.

X. Acute and Chronic Effects of Nicotine. The experimental use of nicotine has failed to produce coronary heart disease in animals that are similar in form to humans. The pharmacological action of nicotine can be attributed to stimulation of autonomic ganglia and the release of catecholamines. However, neither mode of action individually has been demonstrated to produce

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coronary insufficiency, experimental hypertension, atherosclerosis and thrombosis. Hyperlipidemia can be induced by catecholamines or nicotine but these same agents do not produce atherosclerosis unless the animal has also been fed a diet high in cholesterol.

XI. Circulatory Effects of Carbon Monoxide. The mean carboxyhemoglobin content of the blood of smokers is 3.76% saturation, which is elevated to a mean level of 5.26% during smoking. About half of the former value is due to carbon monoxide present in the atmospheric air. Acute exposure to carbon monoxide, resulting in 10% saturation, does not influence heart function. Chronic exposure of animals to carbon monoxide results in atherosclerosis, but there are no functional studies to support the contention that in these cases the heart is ischemic.

XII to XIV. Secondary Publications. These sections include the page by page critique of the US Public Health publications on "Smoking and Health." The conclusions contained in them have been cited in numerous articles. In only a few of these has the validity of the conclusions been questioned.

XV. Recommendations. The author has listed the nature of future investigations relating to coronary heart disease. The two most important areas are: (1) identification of patients with tobacco angina, as distinct from effort angina in prospective studies and (2) measurement of cardiac function in animals chronically exposed to cigarette smoke, nicotine or carbon monoxide. There is so much investigative work already completed that it is needless to repeat or expand twin registries, surveys of selected

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occupational groups, and investigation of acute effects of cigarette smoke in animals and human subjects.

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PART TWO

CORONARY HEART DISEASE

I. Angina Pectoris

II. Myocardial Infarction

III. Atherosclerosis

The term coronary heart disease includes three disease entities. Angina pectoris and myocardial infarction are diseases which can be diagnosed clinically. Atherosclerosis denotes the pathological lesion which is manifested clinically as angina pectoris, myocardial infarction, thromboangiitis obliterans and stroke.

The observations on patients manifesting coronary heart disease in general, and angina pectoris, myocardial infarction and atherosclerosis in particular, are discussed in Sections I, II and III. The selection of the literature was guided primarily to determine the extent of the effect of cigarette smoking in patients. This was readily found in articles summarizing patients investigated clinically or postmortem. The search of the literature was extended to determine the influence of smoking on the prognosis. The information was limited only to myocardial infarction and was not obtainable for the other diseases. The role of cigarette smoking in the causation of these diseases could not be determined. Patients suffering from the said diseases were also exposed to other risk factors, so that it was not possible to identify the contribution of cigarette smoking exclusively.

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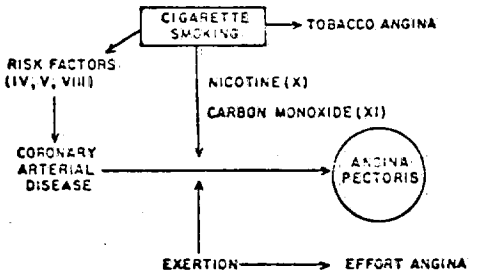
I. ANGINA PECTORIS



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Angina pectoris is discussed in this section only in the following terms: the role of cigarette smoking in precipitating or provoking the anginal attack. In this regard, there are two forms of angina, namely, tobacco angina, in which pain and electrocardiographic signs of coronary insufficiency appear during smoking, and effort angina, in which exertion triggers the appearance of pain accompanied by electrocardiographic signs. The former is rare. In the more common form of angina, i.e., effort angina, there is no clear-cut evidence that cigarette smoking, together with exercise, precipitates the attack.

There are other considerations relating to the role of cigarette smoking in angina pectoris which are discussed in other sections, namely: pathogenesis of atherosclerosis (Section III), incidence of smokers in deaths attributed to coronary heart disease (Section IV) and in morbidity statistics (Section V), interplay of smoking with other risk factors causing

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coronary heart disease (Section VIII), and the influence on the heart of cigarette smoking (Section IX), nicotine (Section X) and carbon monoxide (Section XI). Consideration of all aspects of angina pectoris indicates that cigarette smoking is one of many risk factors and that it can be implicated only in the rare cases of tobacco angina discussed in this section.

There are two bibliographic lists which discuss the general aspects of angina pectoris and the coronary circulation. The articles contained in these lists do not relate directly to the investigation of cigarette smoking but provide background information on the disease under consideration.

List No. 1. Angina pectoris: clinical aspects.
List No. 2. Coronary circulation: clinical evaluation.

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ANGINA PECTORIS: CLINICAL ASPECTS

	Reprint
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CEDERLÖF R, FRIBERG L and LUNDMAN T: Rökning och angina pectoris -- en replik. Lakartidningen 65: 4516-4517, 1968.	A 2
CHARMS B L: Pathophysiology of cardiac symptoms. In: Cardiovascular Disorders. F. G. Davis Co., Philadelphia, pp. 160-176, 1968.	A 3
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THÍSEUS S and TIBBLING L: Angina pectoris eller angina cardiae? Läkartidningen 67: 168-169, 1970.	A 18

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WARREN J: Remarks on angina pectoris. N Engl J Med 266: 3-7, 1962. A 19

WRIGHT H B: Examining the individual in relation to his environment. Bull N Y Acad Med 44: 346-365, 1968. A 20

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Additional Bibliographic List No. 2

CORONARY CIRCULATION: CLINICAL EVALUATION

	Reprint
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BRACHFELD N, BOZER J and GORLIN R: Action of nitroglycerin on the coronary circulation in normal and in mild cardiac subjects. Circulation 19: 697-704, 1959.	A 22
BURCH G E and DePASQUALE: Hematocrit, viscosity and coronary blood flow. Dis Chest 48: 225-232, 1965.	A 23
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ROWE G G, THOMSEN J H, STENLUND R R, McKENNA D H, SIALER S and CORLISS R J: A study of hemodynamics and coronary blood flow in man with coronary artery disease. Circulation 39: 139-148, 1969.	A 32

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I-A. Tobacco Angina

Angina pectoris as a clinical entity was first described by Heberden in 1768. The disease was exceedingly rare, since at the time of the original description Heberden had seen only 20 cases despite having been in practice for 29 years (see Heberden, 1802). The first suggestion that angina pectoris is caused by the use of tobacco was made by Gelineau (1862), who was the ship's surgeon for "Embuscade." After being at sea continuously for almost 4 years, 14 men developed angina pectoris, which Gelineau explained was due to the use of tobacco. Reviewing the evidence later, Kohn (1926) concluded that these cases of angina were actually caused by lead poisoning.

1. Early cases. In 1862 and 1863 Beau reviewed several cases of angina pectoris, which can properly be called tobacco angina. The pain was caused or precipitated by smoking and disappeared when smoking was stopped. The symptoms may soon fail to appear after discontinuance of tobacco use (Bureau, 1907; Mitchell, 1908; Stevens, 1917; Keller, 1922; Wilson and Johnston, 1939). According to others, the symptoms may continue for weeks or months (Brown, 1896; Pardee, 1921; Moschcowitz, 1928; Smith, 1943). The syndrome has also been termed tobacco angina pectoris (Brooks, 1915; Romberg, 1925), nicotine angina pectoris (Furbinger, 1926b), and tobacco heart (Bruce, 1901; Mitchell, 1908). The most characteristic symtom of tobacco angina is precordial pain (Ortner, 1911; Gilfillan, 1912; Cornwall, 1934; Goldston, 1937).

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2. Recent cases. The literature on tobacco angina up to 1944 has been reviewed by Pickering and Sanderson. The most recent review was completed by von Ahn (1960), who differentiated two types of tobacco angina: pain not associated with smoking and that directly caused by smoking. Only the latter type is regarded as tobacco angina by other authors. Krýsa (1966) has predicted an increasing incidence corresponding to the number of smokers over the past 20 years. There has been no attempt to identify such patients in surveys of cases of angina pectoris.

Oram and Sowton (1963) reviewed the literature on tobacco angina and collected 14 previously reported cases in which electrocardiograms had been taken and compared them with 3 of their own cases. These 3 patients were selected from 309 smokers suffering from angina, indicating an incidence of 1%. From a study of 17 patients with tobacco angina, Oram and Sowton could clearly differentiate five syndromes, which were as follows:

a. Angina pectoris with the electrocardiogram at rest usually abnormal. Smoking and exercise induce both pain and electrocardiographic changes of coronary insufficiency within a few seconds. The syndrome was reported for the first time by Huchard (1899).

b. Angina pectoris with pain exacerbated during period of smoking. However, smoking does not induce immediate pain or electrocardiographic change (Albutt, 1915).

c. Angina pectoris with no exacerbation of pain while smoking at rest.

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However, pain may reappear if patient smokes immediately after exercise-induced pain has disappeared (Pickering and Sanderson, 1944). Exercise immediately after smoking induces greater pain and more severe electrocardiographic signs of coronary insufficiency than the same exercise prior to smoking (Moschini-Antinori and Solinas, 1951).

d. No effort angina with electrocardiogram at rest and after exercise normal. Only smoking induces within a few seconds both anginal pain and electrocardiographic changes of coronary insufficiency. This syndrome was referred to as pure tobacco angina by Bryant and Wood (1947).

e. No effort angina but persistent dull precordial discomfort, ectopic beats, paroxysmal tachycardia and dizziness. While smoking the usual amount, there is persistent decreased amplitude of the T wave without depression of the S-T segment. This syndrome is tobacco heart, reported by Russek et al. (1955).

3. Mechanism of tobacco angina. Three theories have been proposed. They are not mutually exclusive and there is a considerable amount of overlapping.

a. Underlying predisposition to angina. Pardee (1921) conceived that tobacco produced angina by acting upon an already formed basis of disease, which was not sufficiently marked to produce symptoms by itself alone.

b. Nicotine-induced angina. The absorption of nicotine sufficient to cause coronary spasm has been suggested by Pawinski (1914),

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Buinewitsch (1940) and Bryant and Wood (1947). The nicotine produces spasm by vascular changes (Blanc, 1925), by stimulation of the cardiac nerves (Maine, 1902; Brooks, 1915) or by reflex vasospasm (Keller, 1922). Oram and Sowton (1962, 1963) induced the syndrome in patients with tobacco angina by intravenous injection of nicotine. Nicotine induces angina not by vasospasm but by releasing catecholamines, which increases the demand for oxygen by the heart. Arai et al. (1951) reported a case of tobacco angina in which the use of vasodilator drugs resulted in the nonoccurrence of angina. These drugs antagonized the effects of nicotine on the heart.

c. Allergy to tobacco. Sensitization to tobacco was proposed by Brooks (1915) and Duerfeldt (1945). The possibility that the heart is the target organ for allergy which is manifested by angina is reviewed elsewhere, in the section dealing with tobacco allergy (Section III-B).

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I-B. Effort Angina

There is an impression among some cardiologists that many coronary patients develop angina on less provocation from exertion after smoking cigarettes. Aronow et al. (1968) selected 10 patients with classical angina pectoris due to coronary artery disease, who performed on a bicycle ergometer until they developed the first manifestation of angina pectoris. All subjects developed angina sooner if they smoked before exercising. The average shortening of the exercise period before angina developed in the smoking state as compared with the nonsmoking state was 24% and the range was 8 to 35%. With the smoking of low-nicotine filter cigarettes, the exercise period before angina developed was shortened by an average of 14% after smoking (Aronow and Swanson, 1969).

The above reports have been interpreted to apply to a majority of anginal patients. It should be recalled that the investigators did not examine more than 10 patients. There is information relating to frequency as well as other facts indicating that cigarette smoking does not provoke effort angina and does not produce coronary vasospasm in such patients.

1. Incidence of tobacco as a precipitating factor in angina pectoris.

In the preceding section devoted to tobacco angina, the review article of Oram and Sowton (1963) was cited as the most recent compilation of reports of cases of tobacco angina. These cardiologists sent a questionnaire to 721 patients, all of whom had had undoubted angina pectoris. The patients

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were asked whether, in their opinion, smoking had any effect on their chest pain. The results were as follows:

534 replies: 58 had died; 167 were nonsmokers and 309 smokers.

309 smokers: 20 experienced angina pectoris shortly after lighting a cigarette.
tobacco
3 with/angina: confirmed by electrocardiogram that cigarette smoking causes signs of coronary insufficiency.

Incidence of tobacco angina is 1 % for anginal patients who smoke and 6 % for all anginal patients comprising smokers and nonsmokers.

The 20 patients who considered that their chest pain was precipitated or aggravated by smoking were reexamined clinically and in each case electrocardiograms were taken, as follows: A resting 12-lead record was first made. Either after the patient had smoked until pain was induced, or after three cigarettes had been smoked consecutively, the electrocardiogram was repeated. A maximum tolerance exercise test was then performed, and at its conclusion a third record was taken. The patient was at once asked to smoke again, and a further record made. After a rest of about 45 minutes a second maximum tolerance electrocardiogram was taken. Electrocardiograms were performed in this manner so as not to miss any of those rare patients in whom smoking will cause a recurrence of chest pain, recently induced by exercise, only when it has just worn off, and also patients in whom, immediately after smoking, pain and electrocardiographic changes on exertion are more severe.

By this manner of investigation, only 3 patients showed

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electrocardiographic changes appearing after smoking and exercise. The incidence of chest pain precipitated by smoking was 6% (20 out of 309 cases) in anginal patients who were smokers, and the frequency of development of electrocardiographic signs of coronary insufficiency in patients during exercise and smoking was 1% (3 out of 309 cases).

2. Coronary arteriogram. The effect on the coronary arteries of the smoking of cigarettes has been investigated in man by arteriography. Likoff et al. (1964) tested the smoking of 2 cigarettes in each of 10 patients with coronary heart disease. No effect on the size of the vessels was observed by cineradiography.

The results of coronary arteriography in patients with angina pectoris did not show a relationship consistent with the amont of cigarette smoking. Newton et al. (1970) examined 80 patients with angina pectoris and made the following observations:

43 normal arteriograms: 29 subjects were smokers.
46 abnormal arteriograms: 40 subjects were smokers.

They concluded that smoking was related to the anatomical findings at coronary arteriography.

Banks et al. (1971) examined 107 patients with ischemic heart disease (66%) and nonischemic heart disease (28%), most of the latter with rheumatic heart disease:

68 cases of ischemic heart disease: 39 subjects were smokers.
39 cases of nonischemic heart disease: 14 subjects were smokers.

The arteriogram was scored according to the degree of obstruction of all

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three coronary arteries. There was no correlation between the number of cigarettes smoked and the extent of disease in any of the arteries. Even the total coronary arterial score did not bear any significant relation to the tobacco consumption. There is, therefore, no indication by arteriography that cigarette smoking produces obstructive lesions in patients with heart disease. The significance of coronary arteriograms in the study of coronary heart disease is the subject of a recent Editorial (1971).

3. Cardiovascular effects of cigarette smoking. This topic is discussed in Section IX. It suffices to mention here that there is no difference between responses of patients with angina pectoris and those of normal subjects. Navarro et al. (1964) compared the effect of smoking 1 or 2 cigarettes on heart rate, arterial pressure, blood glucose, serum cholesterol, and urinary excretion of catecholamines in 7 patients with angina and in 7 healthy persons, all habitual smokers. Except for the excretion of catecholamines, no detectable differences were found between the two groups. Pentecost and Shillingford (1964a, 1964b) and Shillingford (1965) noted that the mean heart rate and blood pressure of patients with angina increased to a somewhat lesser extent than was the case with normal subjects. There is therefore no reason to suggest that the response of anginal patients is different from that of healthy subjects.

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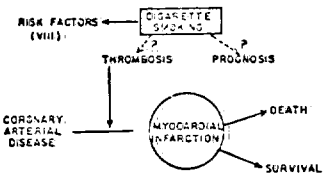
II. MYOCARDIAL INFARCTION



II MYOCARDIAL INFARCTION

A. Controlled Retrospective Studies---------- 33
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Myocardial infarction is a more serious disease than angina pectoris. The association with cigarette smoking is less evident with acute myocardial infarction than with angina pectoris. In this section, the relationship of cigarette smoking to the occurrence of acute myocardial infarction is discussed. It is difficult to identify a cause and effect relation because of the concurrence of other risk factors which are discussed in the remainder of this report. The role of cigarette smoking in initiating the acute infarction and in the prognosis of the patient is examined in this section. The articles on general aspects of myocardial infarction are contained in the following bibliographic lists:

List No. 3. Myocardial infarction: clinical aspects and prognosis.
List No. 4. Myocardial infarction: immediate treatment.
List No. 5. Myocardial infarction: long-term treatment.

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II-A. Controlled Retrospective Studies

The incidence of smoking among patients with acute myocardial infarction can be derived from controlled retrospective studies. There are 9 such investigations from 7 countries which are summarized in Table II-A. The groups range from 79 to 550 patients with clinical diagnosis of acute myocardial infarction. The incidence of nonsmokers ranges from 2 to 34%, with a median of 16% and a mean of 18%. In the corresponding control group, the incidence of nonsmoking ranged from 14 to 44%, with a median of 34% and a mean of 33%.

The lower incidence of nonsmokers or higher frequency of smokers among patients with acute myocardial infarction can also be derived from mortality statistics (Section IV), morbidity statistics (Section V) and examination of selected groups of patients, such as females and young males (Section VI). Cigarette smoking cannot be identified as the most important cause of acute myocardial infarction, because there are other risk factors operative in these comparisons. The following factors have been identified as more important and more frequent than cigarette smoking in the controlled retrospective studies summarized in Table II-A: shortness of stature (Villiger and Heyden-Stucky, 1966), diabetes mellitus (Abou-Daoud, 1968), hypertension (Schwartz et al., 1966) and diet (Kasanen and Forsström, 1966). The retrospective studies have failed to demonstrate that cigarette smoking is the most important risk factor in the pathogenesis of acute myocardial infarction. (Table II-A appears on the next page.)

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Table II-A. Controlled retrospective studies of patients with acute myocardial infarction

Country Investigator	Acute Myocardial Infarction No.	 Smokers %	 Nonsmokers %	Control Nonsmokers %
United States				
Blumer (1934)	150	67	34	34
McCormick (1952)	151	94	6	34
Berry (1960)	60	98	2	44
Finland				
Kasanen and Forsström (1960)	100	84	16	40
France				
Schwartz et al. (1960)	612	86	14	14
Germany				
Schimmler and Neff (1966)	550	81	19	28
Japan				
Hyams et al. (1967)	79	90	10	21
Lebanon				
Abou-Daoud (1968)	91	66	34	43
Switzerland				
Villiger and Heyden-Stucky (1966)	100	75	25	41
		Mean	18%	33%

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II-B. Sudden Death

It has been estimated that death occurs during the first 24 hrs in about 10 % of patients suffering from acute myocardial infarction. No observations have been made which indicate that excessive smoking is the precipitating cause of the acute episode. There are claims that sudden death is more likely to occur among smokers but these are based on the following indirect evidence:

1. Age of patients. Spain et al. (1969) examined a group of 102 men who died suddenly of acute myocardial infarction. The average age at the time of death was 16 years less in those who smoked heavily than it was in the nonsmokers. Porsteinsson et al. (1971) reviewed a group of 119 men and 32 women who died of myocardial infarction. The average age at the time of infarction was 57.9 for smokers, 62.1 for exsmokers and 69.2 for nonsmokers. Spain et al. (1969) have discussed two explanations for the occurrence of sudden death among smokers at a younger age than among nonsmokers. They discounted alteration in coagulability of the blood by smoking on the basis that the incidence of recent coronary arterial thrombi was not correlated with smoking habits. They favor the explanation that smokers as a group are in many respects different types of individuals from nonsmokers (see Section VI). This is supported in their study by the fact that the average age at which those who smoked heavily were involved in and died on account of accidents, suicide and homicide was 9 years less

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than the average age at which nonsmokers died because of similar events.

2. Survival time. Spain (1970) and Spain and Bradess (1970) examined 88 autopsy cases of sudden death following acute infarction. Their results were as follows:

18 nonsmokers:	12 survived < 1 hour and	6 survived > 8 hours (33.3 %)
30 smokers (< 1 pack):	22 survived < 1 hour and	8 survived > 8 hours (26.6 %)
40 smokers (> 1 pack):	38 survived < 1 hour and	2 survived > 8 hours (5.0 %)

Survival time was decreased in the heavier smokers. The association was less evident within the older age brackets and more striking under the age of 50.

Parás Chavero et al. (1970, 1971) reported 106 men who had myocardial infarction. The mortality during the acute episode was as follows:

14 nonsmokers:	2 deaths (14.0 %)
10 smokers (< 1 pack):	1 death (5.5 %)
68 smokers (> 1 pack):	11 deaths (16.2 %)

There was no statistically significant difference in mortality between smokers and nonsmokers.

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II-C. Prognosis

Patients who survive the first 24 hours after acute myocardial infarction have been examined to determine whether cigarette smoking influenced their prognosis. The conclusion has been uniformly negative. Cole et al. (1954) examined 285 patients. Statistics of smoking habits were obtained for nonsmokers and smokers respectively, as follows:

17 nonsmokers	29.4 % died within 2 months	29.4 % lived over 10 years
31 smokers (< 1 pack)	9.6 % died within 2 months	41.9 % lived over 10 years
21 smokers (> 1 pack)	14.3 % died within 2 months	57.0 % lived over 10 years

The above results show that nonsmokers did not have a better prognosis than smokers. In fact, the contrary is suggested, namely, that smokers who develop myocardial infarction are more apt to live longer than nonsmokers.

The duration of survival of patients following an acute myocardial infarction has been examined by two other groups. The Coronary Drug Project Research Group (1969) studied a total of 2,181 men. There was no association between smoking and prognosis. De Soldati et al. (1972) examined 66 cases of acute myocardial infarction and noted the following mean duration of survival:

17	nonsmokers	44.5 months
49	smokers (< 1 pack)	99.6 months
	smokers (> 1 pack)	56.7 months

The differences between groups were statistically significant. It can be noted that the duration of survival of heavy smokers is longer than that of moderate smokers.

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The electrocardiograms of 175 men who survived a year without recurrence after a first myocardial infarct were examined for periods ranging from 1 to 4 years (Cox, 1967). In the absence of recurrence, 10.9% at the end of 1 year and 20.0% at the end of 4 years had a normal electrocardiogram. There was no relation between the return to normal and the extent of smoking after infarction.

The electrocardiogram reflects the severity of infarction and this in turn influences the prognosis. Royston (1972) examined at autopsy the severity of infarction of 200 hearts. The extent of damage was graded in increasing order of I, II and III. The results of that author based on smoking habits that were known for 156 cases, were as follows:

32 nonsmokers:	I 54%	II 42%	III 4%
23 smokers (light):	I 52%	II 43%	III 5%
68 smokers (moderate):	I 62%	II 35%	III 3%
33 smokers (heavy):	I 61%	II 39%	III 0%

The severity of the infarct did not appear to be affected by the smoking habits.

The number of patients involved in all the investigations reported is not great. If additional studies are planned, two important articles should be considered. Seigel and Loncin (1968) reviewed 16 studies of long-term survivorship after a myocardial infarction. They noted that the risk factors that have been studied meticulously by investigators interested in the incidence of the disease have been virtually ignored in the area of prognosis. Hay and Turbott (1970) have surveyed the changes in smoking habits in 370 men after myocardial infarction. They intend to

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use the results of their survey to show whether alteration of smoking habits improves the outlook of a person who has had an infarct. They recognize the difficulty of distinguishing between the effects of abstinence from smoking and other therapeutic measures, such as dietary changes, drug treatment, alteration in the way of life and careful medical supervision.

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II-D. Complications

The two most frequent complications following myocardial infarction are cardiac arrhythmias (Foliguet et al., 1963) and cardiogenic shock (Scheidt et al., 1970). There is no report indicating the influence of smoking on the incidence of these complications. The nature of the cardiac effects of cigarette smoke and its constituents does not contribute to the development of shock or arrhythmias (see Section IX).

A few patients with myocardial infarction have been reported to have malignancy also. Five cases of bronchial carcinoma were described by Buytendijk and Maesen (1964). In an autopsy series conducted by Bergman et al. (1968), there was a negative correlation between atherosclerosis and cancer. Several other articles indicate a negative correlation between these two diseases (Casper, 1932; Dormanns and Emminger, 1934; Sjövall, 1934; Dungal and Benediktsson, 1958). Since there is a positive correlation between smoking and bronchial carcinoma and smoking and myocardial infarction, it is surprising to note that a negative correlation exists between myocardial infarction and bronchial carcinoma.

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II-D. Complications

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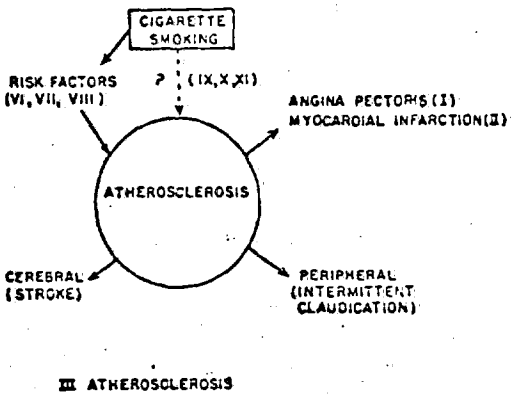
III. ATHEROSCLEROSIS



III ATHEROSCLEROSIS

A. Coronary Atherosclerosis---- 55
B. Peripheral Atherosclerosis--- 60
C. Cerebral Atherosclerosis---- 70

The pathological process underlying coronary arterial disease is atherosclerosis. There is thickening of the arterial wall, which prevents an increase in delivery of blood to the heart proportionate to its demand for oxygen and promotes the formation of a thrombus leading to infarction. The consequences are manifested clinically as angina pectoris (Section I) and acute myocardial infarction (Section II).

Atherosclerosis can extend to the peripheral and cerebral vascular beds, manifested clinically as intermittent claudication and stroke. A high incidence of smoking has been noted in patients suffering from each of these diseases. The predominance of smokers is greatest among patients with peripheral vascular disease, least among those with cerebral disease and in between these for cases of coronary heart disease. The nonuniformity of the relationship between smoking and each of the three forms of

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atherosicerosis can be explained by the differences in risk factors in the pathogenesis of each of these vascular diseases. Hypertension is the most important one for cerebral atherosclerosis, hyperlipidemia for peripheral atherosclerosis, and genetic personality and socioeconomic factors for coronary atherosclerosis. Details relating to these risk factors are discussed in Sections VI to VII.

Cigarette smoking influences the resistance of the blood vessels in each of the three vascular beds. The acute effect is a transient reduction in peripheral blood flow, an increase in coronary blood flow and no significant change in cerebral blood flow. This does not adequately explain the appearance of atherosclerosis in all three vascular beds. The chronic effects of smoking have also been investigated. It has been suggested that cigarette smoking per se or the constituents of cigarette smoke, i.e., nicotine and carbon monoxide, can cause atherosclerosis. The evidence in support of this claim is reviewed in Sections IX to XI.

The articles relating to atherosclerosis in general are contained in the following listing

List No. 6. Atherosclerosis: pathogenesis.
List No. 7. Atherosclerosis: prevention.
List No. 8. Coronary atherosclerosis.
List No. 9. Peripheral vascular disease.
List No. 10. Cerebrovascular disease.

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III-A. Coronary Atherosclerosis

Since atherosclerosis is an anatomical lesion, its diagnosis can be made unequivocally only by coronary arteriography or by postmortem examination of the heart. A cause and effect relationship between smoking and coronary atherosclerosis has not been established. The available information is as follows:

1. Coronary arteriogram. In 89 patients suffering from angina pectoris, among the 46 cases which showed abnormal arteriograms 86% were smokers, whereas among the 43 with a normal pattern of arteriogram 68% were smokers (Newton et al., 1970). There was a slightly higher incidence of smokers among patients with an abnormal arteriogram as compared with those having a normal arteriogram in another series of 73 coronary heart disease patients (Martínez Ríos et al., 1972). In a study consisting of 107 patients with either ischemic or nonischemic heart disease, there was no indication by arteriography that cigarette smoking produces obstructive lesions in the coronary vessels (Banks et al., 1971).

The conflicting conclusions are readily understandable because coronary heart disease may occur in a patient who has a normal arteriogram (Likoff et al., 1967). Furthermore, other risk factors, such as hypercholesterolemia, may also be associated with an abnormal arteriogram (Hultgren et al., 1967). It is difficult to control these factors and prove that smoking is the only variable factor relating to the abnormal arteriogram.

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2. Postmortem examination and influence of cigarette smoke. The results of autopsies performed by various groups indicate an association between coronary atherosclerosis and smoking as well as other risk factors. In 989 consecutive autopsies, a small but definite percentage of heavy smokers of cigarettes developed more marked sclerotic changes in their aortas and tended to have slightly higher blood cholesterol levels than did nonsmokers (Wilens and Plair, 1962). In 1,019 consecutive autopsies, there was a graded and statistically significant increase in the severity of aortic atherosclerosis with increasing use of cigarettes measured by both intensity and duration (Sackett et al., 1968). In 747 autopsied men, atherosclerotic involvement of aortic and coronary arteries is greatest in heavy smokers and least in nonsmokers (Strong et al. / 1969). Of 1,972 men who died of diseases other than coronary heart disease, the percentage with an advanced degree of coronary atherosclerosis was higher among cigarette smokers than among nonsmokers (Auerbach et al., 1965).

In 200 consecutive deaths reported to have occurred from myocardial infarction in Army hospitals, almost all were of smokers but there was also a 50% incidence of hypertension, 46% of obesity and 11% diabetes mellitus (Jacobs, 1968). Of 94 men who had died suddenly from coronary heart disease, aortic atherosclerosis was more extensive among the / cigarette smokers than among the / nonsmokers, but the severity of coronary atherosclerosis was unrelated to smoking habits (Rissanen et al., 1972).

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In 1,150 persons dying violently, the extent of coronary atherosclerosis was unrelated to smoking (Viel, 1968). In a smaller series of 84 violent deaths, both coronary and aortic atherosclerosis were more severe in cigarette smokers than in nonsmokers (Rissanen et al., 1972).

3. Postmortem examination and risk factors. The inconsistent correlation between atherosclerosis and smoking which was so frequently referred to in the preceding paragraphs can be explained by the varying influence of other risk factors. The influence of sex and that of geographical location have been noted by Strong et al. (1966) and by Montenegro and Strong (1968). Other risk factors which have been shown to correlate with atherosclerosis include the following: age (Yater et al., 1951), somatotypes (Spain et al., 1953), race (Groom et al., 1959), behavior (Friedman et al., 1968) and blood cholesterol levels (Nimalasuriya et al., 1971).

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III. ATHEROSCLEROSIS

A. Coronary Atherosclerosis

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III-B. Peripheral Atherosclerosis

Although the primary concern of this review is coronary heart disease, a discussion of peripheral atherosclerosis is included. If peripheral vascualr disease is a manifestation of generalized atherosclerosis (including coronary), it is important to review their relationship to cigarette smoking.

1. Incidence among smokers and nonsmokers. Surveys have been conducted by soliciting answers to a questionnaire or by measuring certain parameters. In the Framingham study described below (Section IV), 5,311 persons were questioned for occurrence of intermittent claudication. Although all were initially free from heart and peripheral vascular disease, in 12 years 51 persons developed unequivocal claudication (Kannel et al., 1965). These individuals were smokers with one or more of the following conditions: hypertensive vascular disease, electrocardiographic abnormalities and elevated blood cholesterol level. In the Tecumseh Community Health Study, the absence of peripheral pulse was noted as an indication of coronary and cerebral arterial disease. There was no correlation between absence of peripheral pulse and cigarette smoking, although a positive correlation was demonstrated for blood pressure, body weight and blood sugar (Johnson and Epstein, 1966).

The measurement of pulse wave velocity has given conflicting results: Kedra and Dmowski (1966) noted a significant reduction among 100 smokers as compared with 100 nonsmokers; however, Schimmler et al. (1967)

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failed to show a statistically significant difference in velocity between 409 smokers, 109 exsmokers and 228 nonsmokers. Isacsson (1972) used venous occlusion plethysmography to diagnose stenosis of iliofemoral arteries. There were 8 subjects suffering from peripheral vascular disease out of 809 participants in the survey. The blood flow capacity of the legs was reduced in direct proportion to tobacco consumption per day.

2. Thromboangiitis obliterans. There is a uniformly high incidence of smokers among patients suffering from thromboangiitis obliterans. Table III-B summarizes the results of 12 surveys conducted in 8 countries. The groups range from 80 to 1,300. The incidence of smokers ranges from 80.1 to 99.6%, whereas the control groups available in 5 surveys had an incidence of 65 to 69.2% of smokers. It has been estimated by Weiss (1972) that about 70% of the cases of the disease are related to the use of cigarettes.

One risk factor in addition to cigarette smoking has been identified as prevalent in patients with arteriosclerosis obliterans. This is an elevation of serum lipids (Juergens et al., 1960; Goodman et al., 1965). Greenhalgh et al. (1971) noted an elevation of the level of triglycerides in 39% of cases, of serum-cholesterol in 15% and of serum-lipid in 44% in a group of 116 patients with arterial disease of the leg. There was no difference in levels between smokers and nonsmokers.

It is an accepted practice to prohibit smoking in patients suffering from peripheral vascular disease (Nilzen, 1959; Corelli, 1966). There is statistical evidence that termination of smoking increased the number of

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patients displaying spontaneous improvement (Mathiesen et al., 1970).

3. Tobacco allergy. Most patients with thromboangiitis obliterans have a positive skin reaction to tobacco extract (Harkavy et al., 1932; Sulzberger, 1934; Green, 1942; Alfano, 1962). However, a positive skin test occurs in the absence of peripheral vascular disease and reflects a hypersensitivity state of the individual to most allergens (Fontana et al., 1959; De Crinis et al., 1960; Fontana, 1960). The incidence of a positive skin test in healthy smokers is about 20 % (Longhin et al., 1960). It has been possible to desensitize an individual who has previously been hypersensitive to tobacco (Zussman, 1968). A rare case of bronchial asthma due to allergy to tobacco has been reported (Blue, 1970).

Harkavy (1956, 1957, 1968, 1970) has written review articles on tobacco allergy in diseases of blood vessels and of the heart. In the latter organ, Halsey (1933) first suggested that tobacco angina may be a form of hypersensitivity. At the same time, Harkavy (1933) reported a positive skin test in response to tobacco extract in patients with angina pectoris. The phenomenon of sensitization of the heart to tobacco extract was demonstrated in the rabbit heart (Harkavy and Perlman, 1960, 1962, 1964). However, the contribution of the allergic process relative to the other mechanisms in the pathogenesis of cardiovascular disease in smokers has not been elucidated.

4. Complications of peripheral atherosclerosis. In the most severe form of atherosclerosis, gangrene is the outcome. There are other

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accompanying lesions in the less severe forms of atherosclerosis which have been noted in smokers.

a. Coronary atherosclerosis. Some patients suffering from angina pectoris have been reported to complain of peripheral vascular disease (Ralli and Oppenheimer, 1928; Unverricht, 1941). More recently, cases involving a combination of myocardial infarction and peripheral atherosclerosis have been reported from France (Schwartz et al., 1965; Jouve et al., 1969), the United States (Eisen, 1966; Olsen et al., 1968), Austria (Reimer et al., 1969), Italy (Moro et al., 1972), Switzerland (Bollinger et al., 1972) and Greece (Aravanis and Corcondilas, 1972). It has been recommended by Tomatis et al. (1972) that coronary arteriography would help in the evaluation of surgical risk in patients with peripheral vascular disease. Atherosclerosis appears in both beds in some patients but the cause of its predominance in either the coronary or the peripheral location is not known.

b. Hematologic factors. Cigarette smoking is known to induce blood clotting and reduce the oxyhemoglobin (see Sections IX and X). There is a high incidence of closure of aortofemoral bypass grafts which has been attributed to excessive smoking (Wray et al., 1971). In some patients with thromboangiitis obliterans, there is an abnormality in oxyhemoglobin dissociation which has also been partly explained by formation of carboxyhemoglobin in the course of smoking (Astrup, 1964; Birnstingl et al., 1967; Kjeldsen and Mozes, 1969).

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c. Gastrointestinal diseases. The splanchnic vascular bed may show manifestations of atherosclerosis and vascular insufficiency. These include duodenal ulcer (Meade et al., 1968; Monson, 1970), polypoid lesions in the colon (Drexler, 1968) and gallbladder disease (Friedman, 1968). The patients in the stated reports also manifest coronary heart disease The role of smoking in the causation of these syndromes is purely conjectural.

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Table III-B, Controlled retrospective studies of patients with peripheral atheroslerosis

Country Investigator	Peripheral Atheroslerosis No.	 % Smokers	Control % Smokers
United States			
Juergens et al. (1960)	478	97	74
McPherson et al. (1963)	119	93	
Lord (1965)	100	92	65
France			
Delahaye et al. (1970)	222		
Germany			
Preuss et al. (1970)	150	87	
Great Britain			
Eastcott (1962)	114	99	
Oldham (1964)	500	99	
Begg et al. (1965)	100	99	79
India			
Razdan et al. (1967)	125	91	
Israel			
Goodman et al. (1965)	80	99	68
Italy			
Giampaglia et al. (1972)	1300	80	
Switzerland			
Widmer et al. (1969)	277	87	69

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III-C. Cerebral Atherosclerosis

The influence of smoking on the prevalence of cerebrovascular disease has not been clearly defined. Hammond (1966) in a prospective study, discussed in detail in Section IV, computed death rates for cerebrovascular disease with smoking habits. Between the ages of 45 and 74, the death rates from stroke for male smokers were 37 to 50% higher than those for male nonsmokers of comparable age. In female smokers the death rates were 38 to 111% greater than those for female nonsmokers. Above the age of 74, the difference in both sexes were much less. In the US veteran study (Kahn, 1966), the death rates from stroke were higher for smokers than for nonsmokers.

The other investigations compare the role of cigarette smoking with other risk factors for atherosclerosis in the prevalence of cerebrovascular disease. In the Framingham study conducted on over 5,000 men and women during a 12-year period, a statistically significant association could not be demonstrated for the excessive development of brain infarction and cigarette smoking. (Kannel et al., 1965). Hypertension is clearly the most important contributor to stroke incidence and the next in importance is the elevation of lipids in the blood (Kannel, 1971; Kannel et al., 1972). The significance of hypertension as a precipitating factor has also been demonstrated in studies made in Indiana (Dyken, 1970 , in California (Paffenbarger et al., 1970, 1971), in Illinois (Ostfeld et al., 1971), and in Japan (Kimura et al., 1972).

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In a controlled retrospective study the high incidence of smoking and that of hypertension were noted in a group of former college students who subsequently died of stroke (Paffenbarger and Williams, 1966; Paffenbarger and Wing, 1967, 1971). Smoking was not a significant factor in retrospective studies conducted in Minnesota (Balow et al., 1966) and in Ghana (Haddock, 1970). There are reports of patients who develop atherosclerosis in the cerebral and peripheral blood vessels (Fogelholm, 1970; Gordon and Kannel, 1972).

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PART THREE

EPIDEMIOLOGICAL STUDIES OF CORONARY HEART DISEASE

IV. Mortality and Morbidity Statistics in the United States

V. Informative Prospective Studies in Foreign Countries

One of the most significant developments in the management of the patient with coronary heart disease is the prevention of risk factors. The identification of the various risk factors which predispose an individual to develop coronary heart disease has been possible through epidemiological investigations completed in the United States and abroad. The general principle involved in such investigations is to select a group of individuals, in whom to determine the prevalence of coronary heart disease and estimate the extent of smoking, the level of blood pressure, and the cholesterol content, and to assess the genetic, dietetic, psychogenic and socioeconomic factors. In some epidemiologic studies, it has been possible by proper selection of subjects to ascertain the importance of some of these risk factors. Sections IV and V supply the details of the results of analyzing mortality and morbidity statistics.

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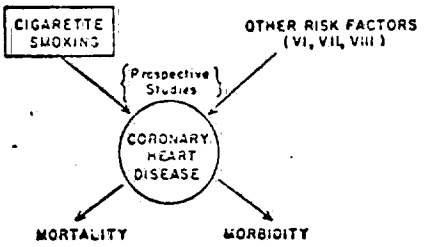
IV. MORTALITY AND MORBIDITY STATISTICS IN THE UNITED STATES



XX PROSPECTIVE STUDIES (IN U.S.A.)

A. Initial Prospective Studies---- 78
B. Other Prospective Studies---- 88
C. Critique of Mortality Statistics---------- 96

The most widely quoted reason for the belief that cigarette smoking causes coronary heart disease is that the mortality and morbidity rates are higher for smokers than for nonsmokers. The results of prospective studies of selected groups of individuals form the basis of this statement. The design and conclusions of three early studies relating to mortality caused by coronary heart disease are discussed in this section.

The association between cigarette smoking and coronary heart disease revealed in surveys does not establish a cause and effect relationship. There are other risk factors that are known to occur in individuals with coronary heart disease, which are difficult to exclude. In properly designed prospective studies it has been possible to exclude one of the risk factors, so that the role of cigarette smoking has been identified with some certainty.

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The special studies are discussed in another section (Section V).

The majority of prospective studies are omitted from this section. They appear elsewhere, because the results relate to the importance of risk factors other than cigarette smoking (see Sections VI to VIII). The general articles relating to epidemiology of coronary heart disease are contained in the following list:

List No. 11. Epidemiologic Techniques.

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Additional Bibliographic List No. 11

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IV-A. Initial Prospective Studies

The Surgeon General's Report on "Smoking and Health," which appeared in 1964, contained the results of three prospective studies conducted by the American Cancer Society, the Veterans Adminstration and the Framingham Group respectively. In subsequent years the follow-up of subjects by the last-mentioned group has led to a revision of conclusions based on the results of the two other studies.

Additional prospective studies have been completed in the following countries: Argentina, Australia, Austria, Belgium, Canada, Czechoslovakia, Finland, France, Germany, Great Britain, Greece, India, Iceland, Israel, Italy, Japan, Netherlands, New Zealand, North Africa, Norway, Peru, Philippines, Puerto Rico, South Africa, Sweden, Switzerland, USSR and Yugoslavia. The results are described in Sections IV to VIII and most of the studies are summarized in Table VII-E.

1. American Cancer Society. Beginning in 1951, over 22,000 volunteers interviewed residents in nine states, using a questionnaire prepared for the American Cancer Society. The follow-up study of 187,766 men was performed after 20 months (Hammond and Horn, 1954), after 34 months (Hammond and Horn, 1958a, 1958b), after 44 months on a larger group of 442,094 men (Hammond, 1964), and after 60 months on 804,409 men

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(Hammond and Garfinkel, 1969). Twenty percent of the million men and women enrolled in the study have not been included in these summaries nor in other articles by Hammond (1958, 1960, 1962, 1963, 1968a, 1968b) and by Hammond and Garfinkel (1966, 1969). The results of the survey have been publicized in the US Public Health Reports on "Smoking and Health," which are reproduced and commented upon in Section XIV. The conclusions are once more noted here for comparison with those from other prospective studies.

a. High incidence of death from coronary heart disease. After 44 months 2,665 men died, the cause of death in 1,388 (52.1%) being coronary artery disease. After 60 months the deaths due to coronary artery disease totaled 14,819.

b. Influence of smoking. The death rate from coronary artery disease was directly related to the amount of cigarette smoking by the individual. Among men in all age groups and women under the age of 70, coronary heart disease death rates were much higher in cigarette smokers than in nonsmokers. The highest mortality rate of 5.6% was for the group of men who smoked 40 or more cigarettes a day as compared with the nonsmokers. Within groups of men who were alike in respect of age, relative weight and blood pressure, coronary heart disease death rates increased with the amount of cigarettes smoked.

c. Risk factors. In an analysis of risk factors, death rates for coronary heart disease were combined with those for stroke and aortic

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aneurysm. The combination of diabetes and a history of high blood pressure is predictive of extremely high death rates. The combination of obesity and cigarette smoking is predictive of high death rates, and that of heavy smoking and a history of high blood pressure of even higher death rates. The predictive death rates for cigarette smoking alone has not been calculated.

2. Veterans Administration. In 1954, the causes of death among policyholders of US Government life insurance were analyzed. The mortality experience of 200,000 policyholders for 2 years was summarized by Dorn (1958), 1959). The ratio of men dying of cardiovascular disease was 1.40 for smokers as compared with nonsmokers.

3. Framingham Heart Disease Epidemiology Study. In 1950 an epidemiologic study was begun in Framingham, Mass., and observations have been made on 5,128 adults, who were examined biennially by physicians for a period of up to 16 years. The conclusions reached in follow-up studies made at intervals of an increasing number of years are noted below.

Four-year follow-up. There was variability of attack rates, so that it was not possible to make generalizations on morbidity and mortality in heart disease. The data suggest that the association of heart disease with smoking is not as strong as that shown with elevated blood pressure, weight and cholesterol (Dawber, et al., 1957).

Six-year follow-up. Smoking was associated with an increased incidence of nonfatal myocardial infarction and of death from coronary heart disease in men aged 45-62. It was not associated with an increased

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incidence of angina pectoris. Cholesterol levels were higher among cigarette smokers than among nonsmokers and were also higher among those who had smoked and stopped than among those who had never smoked. Neither weight not blood pressure showed a similar association with smoking (Dawber et al., 1959).

Eight-year follow-up. Heavy cigarette smokers experienced a threefold increase in the incidence of myocardial infarction and in death from all causes as compared with nonsmokers, pipe and cigar smokers and former cigarette smokers. Cigarette smoking is apparently unrelated to the incidence of angina pectoris. Former smokers and cigar and pipe smokers have morbidity and mortality experiences similar to those of individuals who have never smoked (Kagan et al., 1962).

Ten-year follow-up. Observations in the Framingham Study of 5,128 subjects for periods of ten years indicate that many personal characteristics are related to the development of coronary heart disease. The major risks appear to be elevation of the serum cholesterol level and elevation of blood pressure, though there are several other contributing factors. Combinations of factors further augment the risk and characterize a highly susceptible subject. Recommended beneficial changes in these factors appear to be warranted, particularly in persons exhibiting one or more high-risk traits. (Dawber and Kannel, 1962a, 1962b; Dawber et al., 1962, 1963; Kannel et al., 1962b; Revotskie et al., 1962; Dawber, 1963.)

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Twelve-year follow-up. After a decade, every 10th man and every 20th woman developed coronary heart disease; in the men it resulted chiefly in myocardial infarction or sudden death, in the women chiefly in angina pectoris.

In order to assess the importance of several risk factors, the incidence of coronary heart disease in a group with a definite value (e.g., cholesterol 210-220) (observed cases) was divided by the incidence of coronary heart disease in a group of the same age and sex distribution but with a random cholesterol value (expected cases). The figure resulting from this division x 100, the morbidity ratio, varied with the following risk factors:

		MR
Cholesterol	<200 mg %	55
	>260 mg %	178
Systolic blood pressure	<120 mm Hg	45
	>180 mm Hg	178
Vital capacity	>4 litres	81
	<3 litres	128
ECG anomalies	none	91
	present	203
Overweight	none	50
	present	241*
Cigarette smoking	nonsmoker	69
	20 cgs/day	158

* angina pectoris only

(Dawber, 1963; Dawber et al., 1963a, 1963b; Friedman et al., 1967; Kagan et al., 1963; Kannel et al., 1965, 1966, 1967; Oberwittler, 1968; Truett et al., 1967.)

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Fourteen-year follow-up. Risk of every manifestation of coronary heart disease, including angina, coronary insufficiency, myocardial infarction and sudden death, was distinctly and impressively related to the antecedent level of both systolic and diastolic blood pressure. Risk was not solely related to "hypertension" but was proportional to the level of the blood pressure—even at nonhypertensive pressures—from the lowest to the highest recorded. Also, risk appeared to be related to casual as well as mean basal pressures.

Risk of coronary heart disease over 14 years was examined prospectively in 2,845 women according to their antecedent cholesterol and lipoprotein status. In women under 50 years of age high cholesterol values, as in men, were associated with an increased risk of coronary heart disease and this was true even when adjustment made for concomitant pre-beta lipoprotein and other factors related both to coronary risk and to blood lipid content. In women over 50, however, triglyceride-rich pre-beta lipoprotein was superior to cholesterol for identifying potential coronary cases. Risk of coronary heart disease in women is better estimated by cholesterol under the age of 50 and by pre-beta lipoprotein, or by inference endogenous triglyceride, after that age. (Gordon and Kannel, 1971; Kannel, 1970; Kannel and Castelli, 1972; Kannel and McNamara, 1964; Kannel et al., 1969.)

Sixteen-year follow-up. Cigarette smoking appears to be one of the important risk factors among men for coronary heart disease and cerebrovascular and peripheral vascular disease. For women it is important

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only as a factor related to intermittent claudication. Cigarette smoking bears little relation to angina pectoris. Of all the key factors, cigarette smoking is the only one whose relative role is enhanced in multivariate analysis—that is, when the other risk factors are considered at the same time. From a biological point of view, it is conceivable that the presence of other atherosclerotic factors is a precondition for cigarette smoking to affect atherosclerotic outcomes, but there is nothing in the statistical analysis bearing on this question (Kannel and Gordon, 1971a, 1971b).

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IV-B. Other Prospective Studies

Fifteen additional prospective studies have been completed in the United States. The design and results are summarized in Table IV-B. The important conclusions are as follows:

1. Myocardial infarction. All the studies show a high incidence of smoking in patients who develop or die from myocardial infarction.

2. Angina pectoris. Like the Framingham Study, the prospective studies reported by the Albany Group and the Western Collaborative Group did not reveal an association between cigarette smoking and angina pectoris. It is unfortunate that most prospective studies have pooled angina pectoris and myocardial infarction into a single disease entity, so that it was not possible to differentiate their respective relationships to smoking.

3. Other risk factors. The prospective studies indicate that, in patients with coronary heart disease, other risk factors are as frequent as cigarette smoking, if not more so. The factors which have been identified include blood pressure, blood cholesterol levels, diet, physical activity, race and behavior patterns.

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Table IV-B. Later prospective studies

Investigation and Design	Affect of Cigarette Smoking	Other Risk Factors
New York Health Insurance Plan 110,000 persons questioned from 1961 to 1964. Frank 1968 Frank et al.; 1963, 1966 Shapiro et al.; 1965, 1969, 1963 Weinblatt et al.; 1968a, 1968b	Male cigarette smokers have twice the risk of sustaining a first myocardial infarction shown by nonsmokers. Cigarette smoking is also associated with a doubling in risk for angina among men. Women who smoke cigarettes have twice the incidence rate of first infarction shown by nonsmokers; no difference in the risk for angina.	Physical activity. Body weight 15% or more above average. Race.
Albany, New York 1,838 men examined 1953 to 1955. Doyle et al.; 1959, 1962, 1964	Heavy cigarette smokers experience a similar risk of myocardial infarction compared with nonsmokers. Increased risk or death was associated with cigarette smoking in all combinations of high and low systolic blood pressure and cholesterol levels. Risk of angina pectoris is unrelated to tobacco habit.	
Pennsylvania and Massachusetts College Graduates 1,146 coronary decedents compared with 2,292 classmates. Paffenberger et al., 1966 Paffenberger and Wing, 1969 Thorne et al., 1968	Cigarette smoking and nonparticipation of sports were associated with 50% increase of coronary death.	Systolic blood pressure shorter body stature.
Philadelphia Periodic Health 350 examined who died compared with their living counterparts. Schor et al., 1964a, 1964b	Among those who died of undetermined coronary heart disease, the only finding that clearly discriminated between them and living counterparts was heavy smoking.	
Evans County, Georgia 3109 persons examined 1960-1962 Cassel 1971a, 1971b Garrison et al., 1966 McDonough et al., 1965a, 1965b Kleinbaum et al., 1971	Cigarette smoking could not explain the difference in prevalence of coronary heart disease between Negroes and whites.	Blood cholesterol level. Physical activiy. Race.

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Investigation and Design	Affect of Cigarette Smoking	Other Risk Factors
Teumseh, Michigan 8,641 persons around 1956-1960. Chiang et al.; 1969, 1970 Epstein 1967 Epstein et al., 1965 Higgins and Kjelsberg 1967 Higgins and Keller 1970	Smoking has no influence on prevalence of coronary heart disease on initial examination of subjects. Smokers have lower weight, lower diastolic blood pressure and serum uric acid. Incidence of sudden death in persons with antecedent ventricular premature systoles are independent of smoking habits.	
Chicago Board of Health 1,329 men observed for 9 years. Berkson et al., 1960 Kjelsberg and Stamler 1960 Stamler 1964a, 1964b, 1968, Shekelle et al., 1969	Cigarette smoking as a sole factor is associated with a marked increase in risk. Mortality rate for myocardial infarction is 10 times higher than for low-risk groups.	Hypercholesterolemia Hypertension.
Western Electric Co. of Chicago 1,989 men observed for 4 years Paul et al., 1963	Association of cigarette smoking, most of adult life with subsequent development of coronary disease	Elevated blood cholesterol Use of coffee.
University of Minnesota 11.132 for 5 years. 279 for 20 years. Keys et al.; 1971, 1972	Smoking habit and body weight seemed unimportant in predicting heart disease	Age. Systolic pressure. Serum cholesterol. Diet.
North Dakota State Dept. 1,886 males interviewed. Zukel et al. 1959	Higher incidence of coronary heart disease among smokers.	
Navajo Indian 508 adults for 6 years. Fulmer and Roberts 1963	Smoking rare; low incidence of coronary heart disease.	Diet.
Southwestern American Indians 15,905 adults from 1957 to 1966. Sievers 1967, 1968	Cigarette smoking rare; low incidence of coronary heart disease.	
Western Collaboration Group Study 3,000 subjects since 1960. Barron 1968 Jenkins et al.; 1968a, 1968b Rosenman 1968 Rosenman et al.; 1966, 1967a, b, c; 1968, 1970	Fatal cases have higher frequency of smoking; silent infarction or angina pectoris not associated with smoking.	Overt behavior pattern. Hypertension. Abnormal lipoprotein pattern.

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Table IV-B. (continued)

Investigation and Design	Affect of Cigarette Smoking	Other Risk Factors
California Health Survey 68,153 men from 1954 - 1957; death record in 1962. Borhani et al., 1965 Buechley et al., 1958 Drake, et al., 1957 Weir and Dunn 1970.	Increasing risk of heart disease with greater amount of smoking.	
Seventh-Day Adventists 564 patient records in hospitals. Lemon and Walden 1966 Wynder 1958 Wynder et al., 1959	Smoking plays a role in precipitating coronary artery disease in individuals less than 60 years old; incidence less frequent.	

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IV-C. Critique of Mortality Statistics

In accepting mortality statistics of coronary heart disease there are five considerations to support the thesis that cigarette smoking is one of the important risk factors. They are as follows:

1. Death certificate. The reliance on the death certificate to identify individuals who died of coronary heart disease can be criticized as to its accuracy (Beadenkopf et al., 1963). In 1940 Swartout and Webster reported that with patients hospitalized for less than 48 hours before death there were approximately twice as many discrepancies between the designations of the cause of death and the findings of subsequent autopsies as with patients having longer lengths of medical attendance. Moriyama et al. (1958) and Moriyama (1963) suggested that a strong association between quality of diagnosis and length of attendance might be expected, although for technical reasons their findings on this point were inconclusive. Markush and Schaaf (1966) analyzed 405 death certificates and noted that short attendance by the death certifier was associated with cigarette smoking by the deceased. The pattern relating short attendance to smoking suggests that death certificate diagnoses for cigarette smokers may not be comparable with the diagnoses for nonsmokers. The accuracy of epidemiologic studies conducted by the American Cancer Society may be questioned, since the record of occurrence of heart disease was derived from notation on the death certificate.

2. Combining individual diseases into one group. The International

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List of Causes of Death includes the following types of coronary heart disease:

420.0 Arteriosclerotic heart disease, so described (with or without mention of coronary disease or angina pectoris).

420.1 Heart disease specified as involving coronary arteries.

420.2 Angina pectoris without mention of coronary disease.

In practice, the attending physician can make a distinction between angina pectoris and myocardial infarction, so that it is possible to differentiate between the two clinical entities. Most prospective studies pool both into one single entity of "coronary heart disease," and, when the two are differentiated, the association with cigarette smoking is not the same for both. The mortality statistics show an increasing trend toward death from coronary heart disease (Riesman and Harris, 1934; Lew, 1957; Campbell, 1963a, 1963b). With the current practice of using the designation coronary heart disease it has not been possible to state whether this increasing trend related to either angina pectoris or myocardial infarction or to both (Beadenkopf, 1963).

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3. Pooling of geographical areas and occupational groups. The American Cancer Society survey combines geographical areas. There are striking geographic variations in death rates for coronary heart disease (Friedman, 1967). One extreme example was a group of 11,000 employees of cigarette factories, who were heavy smokers, but the 14-year mortality rate resulting from heart disease and other diseases was below that

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reported by the American Cancer Society (Cohen and Heimann, 1962).

4. Participation of risk factors. In prospective studies several risk factors, including cigarette smoking, have been shown to occur in patients with coronary heart disease (Hilleboe, 1957; Spain, 1960; Acheson, 1962; Epstein, 1965; Cornfield and Mitchell, 1969; Hall et al., 1972). The techniques of retrospective studies are varied and have not been standardized. The shortcomings of some of these technical methods have been discussed by Mulcahy (1967) and Weinstein et al. (1964).

5. Etiology of coronary heart disease. Although several risk factors have been identified, there is a possibility that not all have been determined. It was only recently that phenformin, an antidiabetic drug in use for 20 years, was recognized as a cause of coronary heart disease (Tzagournis et al., 1972). The low incidence of coronary heart disease among Seventh Day Adventists has been explained largely by the fact that they are nonsmokers (Lemon and Kuzma, 1969). The possibility that members of the families of this religious order may have inherited a trait that renders them resistant to coronary heart disease has not been excluded. The mortality encountered in alcoholics has been reported to be associated with a high incidence of smoking (Rankin et al., 1969). Excessive drinkers are usually heavy smokers (Bailey et al., 1969). The problems in identifying other risk factors have been reviewed by Syme (1967).

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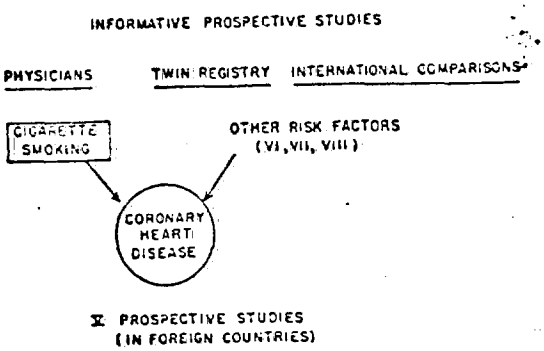
V. INFORMATIVE PROSPECTIVE STUDIES IN FOREIGN COUNTRIES



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C. International Comparisons of Mortality Statistics---------- 111

The prospective studies in foreign countries are essentially similar to those in the United States, which are reviewed in Section IV. However, important modifications have been made in the design of the foreign studies. By the selction of one occupation, i.e., British medical practice, it has been possible to assure a uniform accuracy of answers to a questionnaire. By searching for twins, the importance of inherited constitutional factors has been demonstrated through comparison of the representatives of one occupational group in several countries, the risk factors relative to cigarette smoking in the causation of coronary heart disease have been elucidated. A selection of such prospective studies is included in this section. Other studies are described in Sections VI to VIII in the discussion of individual risk factors. The general articles on epidemiologic techniques are listed as follows:

List No. 12. Epidemiologic studies in foreign countries.

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V-A. Mortality from Coronary Heart Disease of Physicians

Although coronary heart disease had been known to be a "disease of doctors," the first study of its incidence among physicians was reported in 1937 by Smith from the United States. He compared the incidence of coronary sclerosis among physicians, bankers, lawyers, clergymen, laborers and farmers in the clientele of the Mayo Clinic, examining the consecutive clinical records of about 300 persons in each occupational group. The incidence was 10.7% among physicians, whereas in other groups it was less than half that rate, ranging from 2.5 to 5.3%.

A survey of 59,600 British physicians was initiated in October 1951. Questionnaires were sent to them initially and at various times during a period of 10 years. The cause of death of doctors who had replied to the questionnaire and who subsequently died was obtained from the death certificate. The mortality statistics were reported from a follow-up after 29 months (Doll and Hill, 1954), 53 months (Doll and Hill, 1956) and 10 years (Doll and Hill, 1964a, 1964b, 1966).

In the deaths attributed to coronary heart disease or cerebrovascular accident the presence of hypertension was considered. There was no association of smoking habits with the 138 deaths in which hypertension was the primary cause, with the 143 cerebrovascular accidents, nor with the 89 coronary deaths in which hypertension was also mentioned. The only cardiovascular cause of mortality to show any association with smoking habits is coronary disease unrelated to hypertension, and here the

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differences in rates are not marked. The death rate for all smokers (4.08 per 1,000) is 23% higher than that for nonsmokers (3.31) and this excess appears to be limited to the cigarette smokers (4.39). There is no clear gradient with the number of cigarettes smoked but the highest mortality is found among the heaviest smokers. A rising gradient of mortality from nonsmokers to heavy cigarette smokers is clearly present at ages under 65, doubtful at ages 65 to 74 and absent at age 75 years and over. The death rates per 1,000 are as follows:

		Smokers with a daily consumption of:		
Age	Nonsmokers	1-14	15-24	25+ cigarettes
35 to 44	0.11	0.41	0.49	1.50
45 to 54	1.12	1.66	3.40	2.73
55 to 64	4.90	6.81	7.03	8.81
65 to 74	10.83	16.44	13.04	17.59
75 to 84	21.20	21.22	15.04	17.30
85 +	32.35	33.06	58.54	—
all ages	3.31	4.36	4.28	4.97

A second survey of physicians was made, comprising 7,000 British medical practitioners. The respective incidence of coronary heart disease was compared during three periods, namely, 1947 to 1950, 1957 to 1960, and 1961 to 1965 (Meade et al., 1968). The incidence of the first attack of coronary heart disease altered little in the first two periods but increased in the third period. The increase was particularly marked for the 45 to 54 year age group. Although data regarding the smoking habits of doctors were not solicited in the survey, the authors related their results to changes in smoking habits.

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In the United States, a number of surveys have been conducted to determine the association of coronary heart disease. Russek (1960, 1961) noted a high incidence (70%) of smoking among 100 physicians with coronary heart disease as compared with a control group (35%). In a survey of 12,000 men in 14 occupational groups, including physicians, Russek (1965) noted that the incidence of coronary heart disease showed a marked gradient which was unassociated with heredity or diet but strikingly related to the stressfulness of occupational activity. Smoking was not only found to be stress-related but also statistically correlated with the reported frequency of ischemic heart disease. A paradox was noted which casts doubt upon the alleged role of smoking in the genesis of coronary heart disease and adds further emphasis to the probable influence of emotional factors in its causation. Coronary disease was more prevalent among nonsmokers (6.54%) than among exsmokers (2.34%).

Rogers (1965) noted that there was no improvement in mortality from heart attacks among physicians from 1954 to 1964 even though there had been a sharp decline in cigarette smoking during this period. Snegireff and Lombard (1963) recorded the smoking habits of Massachusetts physicians and the death rate among them but did not identify coronary deaths. The mortality rates of physicians in several countries were compared by King (1970) but their smoking habits were not noted. The association between smoking and coronary heart disease has not been investigated in countries other than Great Britain and the United States.

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V-B. Smoking Habits of Twins

The twin registry was established in Sweden to determine whether a constitutional factor predisposes a person to excessive smoking and to diseases. A comparison between the smoking habits of 59 pairs of adult monozygotic twins and 59 pairs of adult dizygotic twins showed significantly greater concordance within the monozygotic pairs (Friberg et al., 1959). These results indicate the importance of the genotype in regard to smoking habits.

The relation of heredity to coronary heart disease in 193 twins was examined by Lundman (1966). The series was small, so that it was impossible to draw definitive conclusions regarding heredity and the disease. In a larger series of 9,168 twin pairs, the studies of a population of first-born twins revealed an increased incidence of angina of 1.50 among male smokers in urbanized areas as compared with smokers in rural districts. No difference between areas was found with respect to nonsmokers; therefore the combination of smoking and the urban factor seems to be associated with the symptom of angina. Smoking as such does not cause angina pectoris, since in smoking-discordant twin pairs there was no difference in morbidity (Cederlöf et al., 1966a, 1966b, 1966c). There was a higher concordance rate among monozygotic twin pairs with regard to angina pectoris than among dizygotic twin pairs, which suggests the existence of a genetic predisposition for the development of angina pectoris (Cederlöf et al., 1967). In 32 pairs of identical male twins with discordant coronary heart disease,

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the severity of coronary heart disease related to psychosocial factors but not to smoking, obesity or blood cholesterol levels (Liljefors, 1970; Liljefors and Rahe, 1970; Lundman et al., 1971). The other results of twin-registry relate to the records of mortality (Friberg et al., 1970; Cederlöf et al., 1970) and of respiratory symptoms (Cederlöf et al., 1967).

An International Symposium (1971) was held in Puerto Rico to discuss plans for twin registries in several countries. In Denmark, analysis or 1,584 pairs of twins revealed a slight and nonsignificant tendency toward coronary infarction to be associated with heavy smoking. Angina pectoris was significantly more frequent in cotwins with a higher significant consumption of tobacco than in those who consumed less tobacco or none at all (Hauge et al., 1970). In 16,000 pairs collected in the United States, the statistics showed an association between smoking and angina. However, it is questionable whether this excess morbidity is causal, since it was not possible to reproduce the association when studying monozygotic smoking discordant twin-pairs (Cederlöf et al., 1969). The appearance of coronary heart disease in identical twins strongly suggest a greater influence linked through the monozygotic inheritance (Sidd et al., 1966; Douglas and Arkun, 1969).

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V-C. International Comparisons of Mortality Statistics

The World Health Organization (1963) has published the cardiovascular disease mortality for various countries. Several comparisons have been made between countries to determine the relationship of smoking to coronary heart disease.

1. Geographic variation in cigarette consumption. Mulcahy et al. (1970) noted a significant positive association between cigarette consumption and coronary heart disease mortality in 21 countries, including the United States, Great Britain, Sweden and Finland. In 15 of these countries, there was a significant association between total cigarette consumption and excess female/male expectation of life, which may be accounted for by the documented or assumed heavier smoking by males. The authors interpreted their results as consistent with, but not proof of, the hypothesis that cigarette smoking is a significant risk factor in coronary heart disease mortality.

2. Importance of blood pressure. The other comparisons considered risk factors not related to smoking in patients with coronary heart disease. In 600 middle-aged men similarly employed in England and in the Eastern United States, the prevalence of chest pain and electrocardiographic evidence of cardiac ischemia are significantly more common among the American men, particularly those over 50 years of age (Reid et al., 1967). The higher blood pressure observed in Americans is readily explained by their greater body weight and skinfold thickness. Although there are differences in smoking habits, it is suggested that factors associated with

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excessive adiposity of the Americans are the more likely explanations of their adverse experience in cardiac disease.

Clerical workers drawn from 5 European countries were examined in a collaborative study (Rose et al., 1968). The results of a standard questionnaire sent to 4,522 subjects and of electrocardiograms in some cases indicate a high prevalence of coronary heart disease in all countries. Cigarette smoking was not associated with prevalence of this disease. An elevated blood pressure was the most consistent risk factor. Higgins et al. (1972) compared miners in the United States with those in Great Britain and concluded that blood pressure, rather than weight and smoking, has the most striking association with prevalence of coronary heart disease. The international comparisons of Reid et al. (1966) and of Stocks (1969) did not include a comparison of blood pressure, cigarette smoking and mortality from coronary heart disease.

3. Importance of blood cholesterol level. The epidemiology of coronary heart disease in 7 countries has been reported by Keys et al. (1970) and have publishe supplements to the Acta Medica Scandinavica and to Circulation. The most consistent theme of the reports is that inhabitants of the geographic areas characterized by serum cholesterol values of approximately 200 mg % have a relative immunity to coronary atherosclerosis and its complications. Cigarette smoking clearly appeared to be a significant risk factor in American railroad employees but this was less certain in the other countries (Paul, 1970).

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C. International Comparisons of Mortality Statistics.

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PART FOUR

RISK FACTORS FOR CORONARY HEART DISEASE

VI. Fixed Risk Factors

VII. Preventable Risk Factors

VIII. Preventable Risk Factors Probably Influenced by Cigarette Smoking

In recent years, the statistics of mortality and morbidity have been cited as supporting the hypothesis that cigarette smoking causes coronary heart disease. The major objection to the use of statistics is that the pathogenesis of coronary heart disease is of a complex nature. There are several risk factors, including cigarette smoking, which are known to predispose individuals to develop coronary heart disease. However, the importance of risk factors relative to cigarette smoking has not been determined.

For the purpose of this review, the risk factors are divided into two groups comprising preventable and nonpreventable or fixed risk factors. The former group has been further divided into those that are probably influenced by cigarette smoking and those that are not. Since most of the literature cited in these sections pertains to the epidemiology of coronary heart disease, the geographical location of each investigation is specified.

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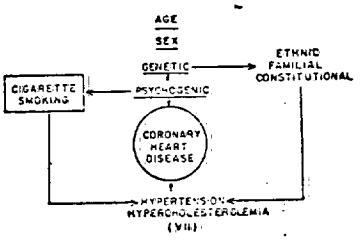
VI. FIXED RISK FACTORS



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C. Genetic Factors------------- 129
D. Psychogenic Factors---------- 134

The prevalence of coronary heart disease is determined by age, sex, and genetic and psychogenic factors. The last two of these are interrelated in that the behavioral pattern of a coronary patient is actually an inherited trait, but it may also be influenced by socioeconomic conditions, discussed in Section VII. The list of genetic factors includes the ethnic group, familial predisposition, and constitutional features. An individual who inherits the predisposition to coronary heart disease is more likely to acquire the smoking habit. The predisposition to develop hypertension and hypercholesterolemia can also be inherited but these are discussed in Section VII, since both factors can be either controlled or prevented.

The articles relating to fixed risk factors are in the following additional bibliographic lists:

List No. 13. Risk factors in coronary heart disease.
List No. 14. Risk factors in coronary heart disease in the young adult.
List No. 15. Stress and psychogenic factors in coronary heart disease.

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VI-A. Age and the Prevalence of Coronary Heart Disease

Coronary heart disease appears more frequently in the elderly (Thould, 1965). It was stated in Section IV that the association between cigarette smoking and coronary deaths is more conspicuous in the younger age group (see also bibliographic List No. 14). This is supported further by the examination of patients under 40 years of age who develop coronary heart disease. Of the 18 investigations listed in Table VI-A, 8 show an incidence of smoking exceeding 90 %. There are 10 reports in which the patients are either nonsmokers or smokers who are less numerous among the controls.

The high incidence of smoking among the young patients developing coronary heart disease does not necessarily mean that cigarette smoking is the cause. The following risk factors have been identified as equally important in the pathogenesis of the heart disease: family history (White, 1935; Roth and Pepe, 1957); lack of exercise (White, 1957); increased blood cholesterol (Gertler et al., 1951; Hatch et al., 1966; Walker and Gregoratos, 1967; Bahl et al., 1970); imparied glucose tolerance (Hatch et al., 1966); mesomorphic body build (Gertler et al., 1951; Roth and Pepe, 1957) Nanda, 1967); obesity (Walker and Gregoratos, 1967); and nervousness (Roth et al., 1967).

There is no survey which indicates that cigarette smoking is the only important risk factor.

(Table VI-A appears on the next page.)

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Table VI-A. Controlled retrospective studies of young male adults with coronary heart disease

Country Investigator	Coronary Heart Disease No.	 % Smokers	Control % Smokers
United States			
White (1935)	28	100	
Gertler et al., (1951)	100	81	76
Roth and Pepe (1957)	20	90	
Hatch et al. (1966)	24	96	70
Roth et al. (1967)	53	87	
Walker and Gregoratos (1967)	100	87	
Sidd et al. (1970)	1	0	
Nizet and Robertson (1971)	1	0	
Czechoslovakia			
Jakuszewska (1969)	22	45	
France			
Bolens and Ferrero (1967)	1	100	
Germany			
Dörken (1967, 1968)	205	99	82
Gsell (1966)	2	100	
Hungary			
Lukl and Weinberg (1963)	31	86	
India			
Mukerjee (1968)	15	33	63
Bahl et al. (1970)	29	52	68
Mexico			
Moleiro and Medina Briceno (1968)	84	74	
Estandia Cano et al., (1971)	84	94	
Poland			
Ciświcka - Sznajderman et al. (1971)	60	97	75

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VI-B. Sex as a Risk Factor

The importance of coronary heart disease as a cause of death in women has been overshadowed by the magnititude of this disease in men. The male to female ratios of coronary deaths range from 2 to 6. In recent years, the total number of females dying from coronary heart disease has been slowly increasing. One cause is the earlier onset of the menarche and of the menopause compared with several decades ago (Mills, 1937). The female gonadal hormone is believed to retard coronary heart disease, and, when estrogen production subsides following the menopause, there is a sharp increase in mortality (Furman, 1968; Klink, 1970; Paulussen, 1970).

Another explanation proposed for the increasing incidence of coronary heart disease is the rising consumption of cigarettes among women (Hartroft, 1956). An examination of women who develop coronary heart disease indicates that there is a wide range of incidence of smoking, from 20 to 90 % (TableVI-B). In the same surveys, the following risk factors have been identified as prevalent in female patients: hypertension (James et al., 1955; Mulcahy et al., 1967a, 1967b; Dörken, 1967), hypercholesterolemia (Oliver, 1971), diabetes (James et al., 1955) and overt behavior pattern (Rosenman and Friedman, 1961). It has not been possible to assess the importance of these risk factors relative to cigarette smoking in females who suffer from coronary heart disease.

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Table VI-B. Controlled retrospective studies of female adults with coronary heart disease

Country Investigator	Coronary Heart Disease No.	 % Smokers	Control % Smokers
United States			
James et al. (1955)	112	20	
Eliot and Bratt (1969)	15	53	7
Rosenman and Friedman (1961)	29	38	45
France			
Jouve et al. (1966)	330	24	14
Germany			
Dörken (1967)	20	90	33
Wink and Hager (1972)	273	60	4
Great Britain			
Mulcahy et al. (1967a) (1967b)	100	63	46
Kenya			
OJiambo (1968)	1	0	

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VI-C. Genetic Factors

The importance of genetic factors in the causation of coronary heart disease has become apparent by the analysis of males of 65 years of age or older who do not suffer from the disease (Brown and Ritzman, 1967). The smoking habits of 133 such individuals compared with those of 100 control patients with heart disease were as follows:

Males without heart disease	Controls with heart disease
40 % nonsmokers	31 % nonsmokers
49 % smokers, inhalers	61 % smokers, inhalers
11 % smokers, noninhalers	8 % smokers, noninhalers
9,550 average pack-years	11,201 average pack-years

It was further noted by Brown and Ritzman that the difference in pack-years between the two groups was not statistically significant. The following factors were found to be associated with this absence: moderate eating habits, regular physical exercise, lack of concern with social status, normal serum total cholesterol levels, and no family history of heart disease. The last three factors can properly be identified as genetic and are discussed in this section.

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Before the individual genetic factors are discussed, it is pertinent to mention other types of investigations relating to the problem. A review of factors relevant to a low prevalence of coronary heart disease in population groups throughout the world failed to identify a consistent pattern of racial or other risk factors (Bruhn and Wolf, 1970). However, twin

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registries established in Sweden and other countries have proven the importance of genotypes in the prevalence of coronary heart disease (see Section V-B). A similar conclusion holds for the hypertension and arteriosclerosis in monozygotic twins (Liebegott, 1965).

1. Ethnic groups. Several reports cited elsewhere in this review indicate the predominance of coronary heart disease in white males compared with black men. The prospective survey conducted by Cassel et al. (1971) in Georgia revealed that, of 143 new cases of coronary heart disease occurring in a seven-year period, the adjusted incidence rate/1,000 was 83 for white and 24 for black males. The females did not show a significant difference, the rate/1,000 being 38 for whites and 34 for blacks.

The South African Bantu and the people of India are less prone to develop coronary heart disease (see review by Walker, 1969).

2. Family history. The hypothesis that coronary heart disease is at least in part a hereditary disorder is based on prevalence studies (Russek, 1959; Meigs, 1966). It has been noted that, by interviewing students, the greates proportion of affected persons was always found among the offspring of 2 affected parents and the smallest among the offspring of 2 unaffected parents (Thomas, 1959). The importance of an inherited predisposition was arrived at by interviewing 75 survivors of myocardial infarction (Rose, 1964), by correlating absenteeism with reported causes of parental death in a group of 98 men, and in a comparison of death rates of individuals with longevity of their parents and grandparents (Hammond et al., 1971).

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In the last-mentioned study, the death rates from coronary heart disease, hypertensive heart disease and stroke were found to be considerably higher among short-lived parents than among subjects with long-lived parents. This was found to be the case for coronary heart disease among men without a history of high blood pressure or diabetes, who were not seriously overweight, who took some exercise and who did not smoke cigarettes regularly.

A comparison of siblings in Boston and Ireland indicated that physical activity, way of life and meal patterns may be associated with the difference in death rates for cases of coronary heart disease in the United States and Ireland (Trulson et al., 1964). The familial history of the subjects was not examined. However, the smoking habits were noted to be similar, i.e., 36 % of Boston samples and 28 % of men in Ireland smoked more than one package of cigarettes daily. The higher death rate in the United States cannot be attributed to smoking.

3. Constitutional factors. The coronary-prone individual is characterized by amphometric features and biochemical changes in the blood. Among the latter, the serum cholesterol level has the highest correlation with coronary heart disease (Gertler et al., 1959). Details of this risk factor are discussed in Section VIII-C. The genetic hypothesis as it relates to coronary heart disease has been reviewed by Thomas (1968).

The relationship of cigarette smoking to constitution has been examined by Damon (1961). Among 167 adult male factory workers of

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Neapolitan parentage but of American birth or upbringing, the lean men smoked significantly more than the fat ones. Smoking was not associated with morphological masculinity. In a study of American-born college students by Baer (1966), heavy smokers were significantly taller than light smokers, former smokers and nonsmokers. The relevance of these observations to coronary heart disease need to be investigated.

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VI-D. Psychogenic Factors

The individual who is prone to develop coronary heart disease has a personality different from those of others. Several review articles have appeared describing the psychologic makeup of patients who have coronary heart disease (see List No. 15). A distinct behavior pattern accompanied by biochemical derangements has been identified in coronary patients by Friedman and Rosenman (1959, 1971), Friedman et al. (1960, 1970) and Rosenman (1971).

It has been suggested that the high incidence of coronary heart disease among smokers can be attributed to one common cause. The personality of the smoker has been examined and found to be different from that of the nonsmokers (McArthur et al., 1958; Lilienfeld, 1959; Eysenck et al., 1960; Matarazzo and Saslow, 1960; Salber and MacMahon, 1961; Dimond, 1964; Thomas et al., 1970). Russek (1964) has used the smoking pattern in the individual to provide an index by which emotional tensions may be relatively assessed. The smoking behavior of offsprings of patients with heart disease has been analyzed (Rappaport et al., 1968). If follow-up studies of offsprings are extended to determine the appearance of heart disease, then the genotype similarities between smokers and nonsmokers will become apparent.

The occurence of psychogenic factors in coronary patients is accompanied by other risk factors, particularly hypercholesterolemia

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(Teculescu et al., 1972; Segers and Mertens, 1972). An estimation of multivariate logistic risk function including personality and smoking habits has been attempted by Halperin et al. (1971).

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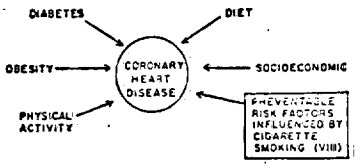
VII. PREVENTABLE RISK FACTORS



XII PREVENTABLE RISK FACTORS (NOT INFLUENCED BY SMOKING)

A. Physical Activity and Exercise- 148
B. Obesity---------- 151
C. Diabetes Mellitus and Sucrose Intake---------- 153
D. Diet and Coronary Heart Disease---------- 157
E. Socioeconomic Factors------- 160

The preventable risk factors are discussed in this section separately from those listed in Section VIII. The two groups can be differentiated by cigarette smoking, since the risk factors included in Section VIII can be influenced by cigarette smoking whereas those listed in this section are not.

Physical activity, obesity, diabetes mellitus, diet and socioeconomic factors are the risk factors which are described in this section. Each one contributes to the pathogenesis of coronary heart disease. The interplay of an individual factor with cigarette smoking is the primary concern of the discussion that follows. The general articles relating to these risk factors are contained in the following bibliographic lists:

List No. 16. Prevention of coronary risk factor.
List No. 17. Exercise in coronary heart disease.
List No. 18. Diet in the causation and prevention of coronary heart disease.

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VII-A. Physical Activity and Exercise

Physical activity and exercise relate to coronary heart disease in a number of ways. The lack of / is a predisposing factor, whereas exercise is a preventive one. In a patient suffering from angina pectoris, exercise initiates an attack and causes an ischemic pattern in the electrocardiogram. In a patient who has developed acute myocardial infarction, exercise properly regulated can influence the prognosis. In a patient developing coronary atherosclerosis, the electrocardiogram recorded during exercise can be helpful in the diagnosis of early insufficiency (see Additional Bibliographic List No. 17).

Cigarette smoking and exercise have been investigated jointly in regard to their influence on the prevalence of coronary heart disease. Frank et al. (1966) reviewed 301 patients with myocardial infarction who were enrolled in the Health Insurance Plan of New York. Smoking did not influence the early mortality rate (death during the first four weeks), whereas physical inactivity was associated with a high mortality rate. Morris et al. (1973) succeeded in training office workers for vigorous exercise and noted that in them the risk of developing coronary disease was about one-third that in comparable men who did not exercise. The smoking habits of men engaging in such activity were similar to those of the other men in the study. That physical working capacity is more important than cigarette smoking as a risk factor has been shown by Wilhelmsen et al. (1969).

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In elderly subjects who had vascular disease as well as in those who did not, an abnormal response to an exercise test was not associated with cigarette smoking (Riley et al., 1970). A similar lack of association was reported among businessmen undergoing a multistage exercise test (Goldbarg et al., 1970). However, in severe exercise, field testing of airmen for 12 minutes showed that endurance performance was inversely related to the number of cigarettes smoked daily (Cooper et al., 1968). There is also a reduction in endurance among long distance runners (Pyörälä et al., 1967; Haas et al., 1970) and among swimmers who are smokers (Pleasents et al., 1966). The electrocardiogram during strenuous exercise has been recorded by Berkson et al. (1966), Merriman (1967) and Recine and Chiavaro (1969). They observed that electrocardiographic changes appeared more frequently among smokers than among nonsmokers. Most of these individuals were healthy. The severity of exercise referred to above does not apply to patients with heart disease.

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VII-B. Obesity

Obesity is a major health hazard because hypertension, nephritis, diabetes, cerebrovascular disease and coronary heart disease occur more frequently in the obese (Stamler, 1959; Whyte, 1965; Stamler et al., 1960). Obesity is not an important associated risk factor in patients dying of coronary heart disease (Keys et al., 1972). Multivariate analysis of the data from 11,000 men in the United States and Europe showed that no measure of obesity made a significant contribution to future coronary heart disease when the factors of age, blood pressure, serum cholesterol and smoking were comparable. In a review of various prospective studies, Heyden et al. (1971) concluded that overweight is a definite risk factor for the development of cerebrovascular disease but not in the etiology of myocardial infarction.

In the prospective study conducted in Evans County, Georgia, the risk of nonsmokers developing coronary heart disease does not increase from the leanest to the moderately overweight and the most obese group. Among white smokers there is an increase in risk with overweight (Heyden et al., 1971). However, these results are not easy to interpret because there is a difference in body weight of smokers and nonsmokers, regardless of the status of the heart. Nonsmokers are heavier than smokers and the difference increases with age (Khosla and Lowe, 1971). Since smoking and obesity are inversely related, studies of the interrelationship of these two risk factors are needed.

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VII-C. Diabetes Mellitus and Sucrose Intake

It has been recognized for more than 35 years that diabetes mellitus predisposes the diabetic to the various manifestations of atherosclerosis, particularly coronary heart disease (Osborn and Goldstein, 1968; Hutchinson, 1970; Moller, 1970). In some of the prospective studies discussed in Section VII-E, diabetes mellitus is an important risk factor in coronary heart disease.

The combination of diabetes and cigarette smoking is suspected of increasing the hazard of the development of atherosclerosis. This has been seen in patients with arteriosclerosis obliterans (Weinroth and Herzstein, 1946; Krosnik, 1967; Kappert, 1971). However, regarding coronary heart disease among diabetics, the additional contribution of cigarette smoking to the severity of the disease has not been demonstrated by control studies. In a survey of 27,000 college alumni, cigarette smoking did not increase the risk of adult onset of diabetes and did increase the risk of coronary disease, but there was no information on the combination of the two diseases (Paffenbarger et al., 1972).

Some patients with myocardial infarction are known to have a decrease in glucose tolerance although they are not suffering from diabetes mellitus (Cohen et al., 1965; Epstein, 1967, 1969; Yudkin, 1967). The plasma-insulin level of patients with coronary heart disease is elevated, so that a deficiency of this hormone is not responsible for the decrease in glucose tolerance (Wahlberg, 1962; Nikkila et al., 1965; Peters and Hales, 1965; Welborn et al., 1966).

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In prospective studies, patients who developed coronary heart disease were found to have consumed more sugar than the control group (Paul et al., 1968; Burns-Cox et al., 1969). It is pertinent to note that in some patients with coronary heart disease there is a strong association between the consumption of sugar and the smoking of cigarettes (Medical Research Council, 1970; Bennett et al., 1970; Elwood et al., 1970). It has been suggested that both risk factors cause myocardial infarction. There is also an inverse relationship between sugar intake and adequate exercise (Richardson, 1972). Cigarette smoking is also known to influence body weight (see Section VII-B). The interplay of several risk factors should be considered when the role of sucrose in the etiology of coronary heart disease is examined in future investigations. The evidence presently available on the theory that sucrose in the diet is a major factor in the development of coronary heart disease has been reviewed by Keys (1971) and Walker (1971).

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VII-D. Diet and Coronary Heart Disease

Experiments on animals have shown that atherosclerosis, including fatal myocardial infarction, has been produced by dietary manipulation. The basic common feature in these experiments is the maintenance of a sustained elevation of the concentration of cholesterol in the blood. Epidemiological evidence indicates that in man the serum cholesterol level is a major factor in the development of coronary heart disease and that the amount and kind of fat in the serum has a major influence on the blood cholesterol level (see reviews by Keys (1962) and Stamler et al. (1963, 1972)). This knowledge has been applied in programs for the prevention of coronary heart disease, and the articles relating to dietary control are contained in Additional Bibliographic List No. 18. The controlled clinical studies by Leren (1966) and Dayton et al. (1969) are noteworthy for providing the unequivocal evidence that a diet low in unsaturated fat reduces the plasma cholesterol level and prevents complications of atherosclerosis in general and of myocardial infarction in particular.

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In the consideration of smoking and coronary heart disease the diet should also be examined. Smokers differ from nonsmokers in taste perception and food preferences. It was reported that the latter preferred bland food and consumed less fat and meat, fewer eggs and more cakes, sweets and chocolate than the former (Krut et al., 1961; Perrin et al., 1961). Among patients with myocardial infarction, liberal coffee drinking, sugar

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intake and smoking were often correlated (Kasanen and Forsström, 1966). The interplay of these dietary factors should be considered before concluding that the high incidence of smoking is the most important risk factor in patients with coronary heart disease.

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VII-E. Socioeconomic Factors

The last group of preventable risk factors are identified under the caption socioeconomic. This includes occupation, education, income level, urbanization, and consumption of alcohol, coffee and other beverages (see reviews by Terris, 1964; Anderson, 1967; Marks, 1967; Hall, 1968; Shekelle, 1968; Cheraskin et al., 1971; Richardson, 1971). Regarding the consumption of alcohol and coffee, Brummer (1969) could not find a significant correlation with coronary mortality in 20 countries. However, in isolated studies there is a correlation between the two. The studies relating to consumption of coffee and alcohol, as well as to other socioeconomic factors, are summarized in Table VII-E. It is not possible to make generalizations, because the conclusions apply only to the particular country involved and need to be confirmed elsewhere. The table has been formulated also to emphasize the interaction of cigarette smoking with socioeconomic and other risk factors in the causation of coronary heart disease. The information contained in the table has been derived from R = retrospective studies, P = prospective studies, and S = single surveys.

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The influence of cigarette smoking on prevalence of coronary heart disease in various occupational groups has been derived from surveys listed in Table VII-E. Haag and Hanmer (1957) reported a four-year survey of the mortality among employees of a tobacco company. There was a higher than average percentage of smokers associated with greater longevity and

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lower death rates from cardiovascular diseases and cancer. Their statistical techniques have been criticized by Case (1958). Most of the objections can be readily overcome by repeating the survey 15 years after it was first completed.

(Table VII-E appears on the following pages.)

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TABLE VII-E.

Role of Socioeconomic and other risk factors in patients with coronary heart disease

Part A. United States

State Investigators and Design	Role of Cigarette Smoking	Role of Other Risk Factors
California		
P = 2,252 employees Chapman et al., 1957		VII-A. Physical activity VIII-B. Hypertension
S = 669 students and family Andrus et al., 1963		VIII-B. Blood pressure
Connecticut		
P = 164 industrial workers Meigs and Albrink 1966		VI-A. Genetic
Delaware		
P = 209 cases of myocardial infarction Pell and D'Alonzo 1958 Pell and D'Alonzo 1970		VII-B. Obesity VIII-B. Hypertension
Georgia		
P = 632 white residents Kaplan et al., 1971		VII-E. Occupational mobility
Hawaii		
P = 42 cases of myocardial infarction Bassett et al., 1969 Bassett et al., 1969 Chung et al., 1969 Bassett et al., 1969 Bassett and Schroffner 1970	Smoking prevalent	VI-A. Race VII-D. Diet VII-E. Alcohol
P = 8,006 men Kagan et al., 1971	Smoking associated with coronary heart disease	VII-A. Obesity VIII-B. Hypertension VIII-C. Hypercholesterolem
Illinois		
P = 784 workers Stamler et al., 1960 Stamler 1959 Stamler et al., 1961		VII-B. Obesity VII-C. Diabetes VIII-B. Hypertension
Indiana		
S = examination of death certificate Morris 1967		VII-A. Physical activity VII-E. Socioeconomic
Maryland		
P = 629 male telephone workers Holland et al., 1967	Smoking not associated with coronary disease	VII-B. Blood pressure VII-E. Ventilatory
P = residents of community with hard water. Constock 1971	Smoking associated with coronary heart disease	VII-E. Socioeconomic

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Massachusetts			
S = 40,000 alumni Paffenbarger et al., 1966	Smoking associated with coronary heart disease	VII-B. VIII-B.	Obesity Blood pressure
R = 600 residents of rural area Pemberton and Macleod 1956	Smoking associated with coughing	VII-E.	Socioeconomic
New York			
P = 1,171 male executives and nonexecutives Lee and Schneider 1958		VII-E.	Socioeconomic
R = 100 young adults with coronary heart disease Russek and Zohman 1958		VI-C. VII-D. VII-E.	Familial Diet Socioeconomic
P = 8,152 males and females Doyle et al., 1968	Smoking associated with coronary heart disease		
R = 200 cases of myocardial infarction and 400 controls Hyams and Loop 1969	Smoking associated with coronary heart disease	VI-A. VIII-B.	Familial Hypertension
P = 260, 430 employees Hinkle 1966 Hinkle et al., 1968 Hinkle 1972		VII-E.	Socioeconomic
P = 110,000 men and women Shapiro et al., 1970	Smoking influences prognosis of coronary heart disease	VII-E.	Socioeconomic
North Carolina			
S = examination of death certificates Tyroler and Cassel 1964		VII-E.	Socioeconomic
North Dakota			
R = 228 urban and rural residents Syme et al., 1964 Syme et al., 1965	Smoking associated with coronary heart disease	VII-E.	Socioeconomic
Ohio			
P = 3,954 attorneys Friedman and Hellerstein 1968		VII-E.	Socioeconomic
Pennsylvania			
P = 1,549 in a German Community Bruhn et al., 1968		VII-E.	Socioeconomic
West Virginia			
P = 1,157 miners Higgins et al., 1969	Smoking associated with coronary heart disease	VIII-A. VIII-E.	Hypertension Ventilatory

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TABLE VII-E.

Role of Socioeconomic and other risk factors in patients with coronary heart disease

Part B. Foreign Countries

Country Investigators and Design	Role of Cigarette Smoking	Role of Other Risk Factors
Argentina		
R = 41 patients with second infarction De Soldati et al., 1971	Smoking prevalent	VII-C. Diabetes
Australia		
P = 3,410 adults in a rural community Welborn et al., 1969	Smoking not related to coronary heart disease	VII-C. Glucose VII-C. Hypercholesterolemia
P = Mass examination in community Cullen 1972	Smoking not compared	VII-C. Glucose tolerance VII-B. Hypertension VII-C. Hypercholesterolemia
Austria		
R = 729 myocardial infarction Reimer and Tiso 1971		VII-B. Obesity VII-B. Hypertension VII-C. Hypercholesterolemia
Belgium		
S = 990 clerks 40 to 59 years old Goossens and Messin 1966	Smoking not related to coronary heart disease	VIII-B. Hypertension VIII-C. Hypercholesterolemia
R = 181 myocardial infarction Deleixhe and Reginster-Hanene	Smoking not related to coronary heart disease	
S = 1,703 residents Meheus et al. 1972	Smoking associated with coronary heart disease	VIII-A. Electrocardiographic signs
Canada		
P = 27,865 individuals Best et al., 1961 Best and Walker, 1964 Best et al., 1967 MacEachen 1966, 1966, 1966	Smoking associated with mortality from cardiac heart disease	
S = 1,000 males 20 to 70 years old Goulet et al., 1968 Goulet et al., 1968	Smoking not associated with coronary heart disease	VI-C. Heredity VII-B. Obesity VIII-B. Hypertension VIII-C. Hypercholesterolemia
Czechoslovakia		
P = 70 patients angina pectoris Stejfa 1967	Smoking does not influence prognosis	
P = various occupations Hloucal and Dušek 1968	Smoking associated with coronary heart disease	VII-A. Farmers VIII-C. Hypercholesterolemia

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Czechoslovakia (Cont.)		
S = 1,213 patients in hospital Horak et al., 1968	Smoking prevalent in coronary heart disease	
P = Questionnaire Santrůček 1970	Smoking not associated with deaths in coronary heart disease	
S = 1,000 autopsies Fingerland et al., 1971	Smoking prevalent in coronary heart disease	
Finland		
R = 683 cases of myocardial infarction Ikkala 1960	Smoking no influence on prognosis	
P = 371 lumberjacks Karvonen et al. 1961	Smoking not related to coronary heart disease	VII-E. Occupation
P = 481 persons older than 65 years old Ruikka 1966	Smoking not associated with coronary heart disease	
P = 1,677 persons in rural areas Karvonen 1962, 1967 Karvonen et al., 1970 Karvonen 1971 Karvonen 1972 Punsar et al., 1969 Punsar et al., 1970	Smoking prevalent	VIII-E. Occupation
S = 1,314 executives Teräslinna et al., 1971 Romo 1972	Smoking related to coronary heart disease	VIII-B. Hypertension
France		
S = 54,460 factory workers Anonymous 1968	Smoking prevalent in coronary heart disease	
R = 100 cases of myocardial infarction Anjuère, 1968	Smoking prevalent in patients	
P = 1,867 residents Himbert et al., 1971	Smoking prevalent in patients with cardiac heart disease	
R = 70 cases of myocardial infarction J. Warter et al. 1972	Smoking rare	VII-A. Unusual effort precipitate infarction
Germany		
R = 170 patients with cardiac heart disease Keiser 1954	Smoking prevalent in patients compared to controls	
R = 550 cases of myocardial infarction Schimmler and Neff 1966 Schimler et al., 1968	Smoking prevalent	VII-B. Obesity VIII-C. Hypercholesterolem
R = 560 autopsy cases of myocardial infarction Crecelius 1966	Smoking prevalent in patients	VII-C. Diabetes VIII-B. Hypertension
R = 30 patients with myocardial infarction Storch et al., 1971	Smoking associated with young patients	VI-C. Psychogenic

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Great Britain		
S = 1,000 men 60 to 70 years old Brown et al., 1957	Smoking not related to coronary heart disease	
S = 1,737 men 50 to 60 years old Edwards et al., 1959	Smoking not related to coronary heart disease	
S = 3,341 male factory workers Lowe 1960	Smoking related to injury and absenteeism	
P = 667 middle aged businessmen Morris et al., 1966	Smoking related to coronary heart disease	VIII-B. Hypertension VIII-C. Hypercholesterolemia
S = 221 pensioners 68 to 85 years old Acheson 1961	Smoking not related to coronary heart disease	VIII-A. Electrocardiogram
R = 536 deaths of myocardial infarction Brown 1962	Smoking related to deaths	VI-C. Familial VII-B. Obesity VII-E. Occupation
S = 200 males below 60 years old Mulcahy et al. 1963 Mulcahy and Hickey 1965 Mulcahy and Hickey 1966 Mulcahy and Hickey 1966	Smoking related to coronary heart disease	
P = Random males 55 to 64 years old Armstrong and Wilson 1964	Smoking not related to incidence of coronary heart disease	VI-C. Constitutional
S = 676 postal workers 40 to 50 years old Reid et al., 1966	Smoking not related to incidence of coronary heart disease	VIII-B. Hypertension
P = 110 patients with myocardial infarction Spelman and Ley 1966		VI-C. Personality does not affect prognosis
P = 54,460 men in industry Brett and Benjamin 1968	Smoking related to mortality from coronary heart disease	
R = 400 male patient below 60 years old Mulcahy et al., 1969	Smoking prevalent among patients with coronary heart disease	VII-C. Diabetes VII-B. Hypertension VIII-C. Hypercholesterolemia
R = 91 male patients under 65 years old Cotton et al. 1972	Smoking prevalent	VIII-B. Hypertension
Greece		
P = 1,300 men in rural areas Aravanis et al. 1967 Aravanis et al. 1970	High incidence of smoking but low prevalence of ECG abnormalities	VII-B. Smokers thinner than nonsmokers.
India		
R = 100 cases with coronary heart disease Bansal, 1970	Smoking prevalent compared to controls	VI-C. Familial history VII-A. Exercise VII-E. Occupation VIII-C. Hypercholesterolemia
R = 1,200 cases of coronary heart disease Vytilingam	Smoking not related to coronary heart disease	VIII-A. Hypertension VIII-B. Hypercholesterolemia

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India (Cont.)		
R = 553 patients with coronary heart disease compared to 1,056 controls Mathur 1960	Smoking not associated with coronary heart disease	VII-E. Socioeconmic class VIII-A. Hypertension VIII-B. Hypercholesterolemi
R = 2,162 cases Jhatakia 1966		VII-E. Socioeconomic factor
S = mortality statistics in various areas Malhotra 1967	Smoking not related to coronary heart disease	VII-E. Socioeconomic
S = hospital admissions Jhatakia et al., 1967	Smoking not associated with coronary heart disease	
R = 450 cases of myocardial infarction Lal and Caroli 1967 Lal and Caroli 1968 Lal and Caroli 1968	Smoking not associated with coronary heart disease	VII-C. Diabetes VIII-B. Hypertension
R = 75 cases of coronary heart disease Chattopadhaya et al. 1968	Smoking associated with coronary heart disease	VI-C. Constitutional VI-D. Behavioral VII-E. Socioeconomic VIII-B. Hypertension
P = 2,030 resident Sarvotham 1968	Smoking not associated with coronary heart disease	VII-E. Socioeconomic
R = 150 cases of myocardial infarction Pandley 1970	Smoking not important risk factor	VII-C. Diabetes VIII-B. Hypertension VIII-C. Hypercholesterolem
R = 240 cases of coronary heart disease Singh and Singh 1971	Smoking not associated with coronary heart disease	VII-C. Diabetes VIII-B. Hypertension
Iceland		
S = Death certificate analysis Sigurjonsson 1969 Sigurjonsson 1969		VII-D. Diet
Israel		
P = 8,500 members in communal settlement Bruner and Manelis 1960		VII-A. Physical activity
P = 331 elderly residents Librach, 1967	Smoking not associated with coronary heart disease	VIII-B. Hypertension
P = 10,059 subjects Medalie et al., 1968	Smoking associated with coronary heart disease	VI-D. Anxiety VII-C. Diabetes VII-D. Diet VIII-B. Hypertension VIII-C. Hypercholesterolemia
Italy		
R = 100 patients with myocardial infarction Palma 1963		VII-E. Socioeconomic
R = 255 cases of myocardial infarction Della Salda et al., 1966	Smoking not associated with coronary heart disease	VI-C. Constitutional

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Italy (Cont.)		
P = 900 men in rural areas Fidanza et al., 1967		VII-E. Socioeconomic VIII-B. Hypertension
S = Analysis of death certificates Malesani 1967		VII-E. Socioeconomic
P = 800 railroad employees Menotti 1967		VI-A. Physical activity
P = 4,668 miners and exminers Casciu et al., 1968	Smoking associated with coronary heart disease	VII-E. Alcohol
R = 450 patient with myocardial infarction Di Cantogno et al., 1968	Smoking prevalent in patients	VII-A. Physical activity VII-D. Overeating
P = 8,000 inhabitants of 2 rural areas Puddu and Menotti 1969	Smoking prevalent in patients with myocardial infarction	VII-A. Physical activity VIII-B. Hypertension VIII-C. Hypercholesterolemia
R = 1,039 females with myocardial infarction Campos and Delneri 1969	Smoking prevalent	
S = 1,737 male laborers Canepa et al., 1968	Smoking prevalent	
R = 530 patients with coronary heart disease Agnese 1970	Smoking prevalent	VIII-B. Hypertension VIII-C. Hypercholesterolemi
R = 386 cases of myocardial infarction De Molo 1970		VII-C. Diabetes VIII-B. Hypertensions VIII-C. Hypercholesterolemi
S = death certificate examination Menotti 1972	Smoking associated with coronary heart disease	VIII-B. Hypertension VIII-C. Hypercholesterolemi
Japan		
P = 1,000 residents in fishing and farming village Kimura 1967	Smoking prevalent	
P = 10,429 residents Johnson et al., 1968	Smoking not associated with coronary heart disease	VIII-B. Hypertension VIII-C. Hypercholesterolem
Netherlands		
S = examination of death certificate Van Voorst Vader 1965	Smoking associated with coronary heart disease	
P = 100 farmers Dalderup et al., 1965 Dalderup 1971		VIII-E. Hypercholesterolemi
R = 34 patients with coronary heart disease	Smoking prevalent	VII-A. Physical activity VII-D. Diet
P = 25,000 residents vanBuchem 1970	Smoking not associated with coronary heart disease	VII-B. Body weight VIII-B. Hypertension VIII-C. Hypercholesterolem
New Zealand		
S = 1,000 males Hunter 1963		VIII-B. Hypercholesterolem

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North Africa		
S = 25 patients with coronary heart disease Bertrand et al., 1971	Smoking prevalent	VIII-C. Hypercholesterolemi
Norway		
P = 62 train drivers Berg and Melkild 1962	Smoking not associated with coronary heart disease	VII-A. Physical activity
P = 4,052 men Zeiner-Henriksen 1971	Smoking prevalent among coronary heart disease	VII-E. Urban factor
Peru		
P = 1,032 residents at high altitude Ruiz et al. 1969	Smoking not associated with coronary heart disease	
Phillippines		
R = 32 cases of myocardial infarction Gutierrez and Dayrit 1969	Smoking prevalent	VIII-B. Hypertension
Puerto Rico		
P = 9,814 urban and rural men García-Palmieri et al., 1970 -Benson et al., 1966	Smoking not associated with coronary heart disease	
South Africa		
P = 600 adult males Bronte-Stewart 1961	Smoking associated with coronary heart disease	VIII-C. Hypercholesterolem
P = 296 elderly Bantu Seftel et al., 1965 Seftel et al., 1970	Low incidence of smoking and coronary heart disease	(Absence of most risk factor
R = 250 cases of myocardial infarction Jacobs 1971	Smoking prevalent	VI-D. Emotional stress VII-B. Obesity VIII-B. Hypertension
Sweden		
P = 973 city residents Tibblin 1970 Tibblin 1968 Tibblin and Wilhelmsen 1971 Tibblin and Wilhelmsen 1971 Wilhelmsen et al., 1972	Smoking associated with coronary heart disease	VII-A. Physical activity VIII-B. Hypertension VIII-C. Hypercholesterolem
S = 3,249 hospital cases Johansson 1968		VII-C. Diabetes mellitus
Switzerland		
P = 3,479 physicians Strobel and Gsell 1965	Smoking associated with coronary heart disease	
P = 500 workers Heyden-Stucki and Schibler-Reich 1967	Smoking associated with hypertension	
USSR		
S = Survey of workers Golubovski 1968	Smoking associated with coronary heart disease	VII-E. Socioeconomic

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USSR (Cont.)		
R = 100 patient with myocardial infarction Borojev and Stanulovic 1971	Smoking prevalent	VII-B. Obesity VIII-B. Hypertension VIII-C. Hypercholesterolemia
P = 1,243 clerks or workers Glazunov et al., 1964		VII-E. Socioeconomic
Yugoslavia		
P = 11,121 Kozarević et al., 1971 Djordjević et al., 1967 Buzina et al., 1967 Djordjević et al., 1970	Low incidence of coronary heart disease	
P = 940 workers Vukadinović and Šarić 1966	Smoking associated with coronary heart disease	VI-C. Constitutional VII-B. Obesity VIII-B. Hypertension

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TABLE VII-E

Role of Socioeconomic and other risk factors in patients with coronary heart disease

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VII. PREVENTABLE RISK FACTORS

E. Socioeconomic Factors

TABLE VII-E

Role of Socioeconomic and other risk factors in patients with coronary heart disease

Part B. Foreign Countries

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Argentina

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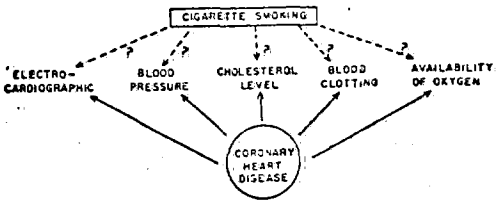
VIII. PREVENTABLE RISK FACTORS PROBABLY INFLUENCED BY SMOKING



XIII PREVENTABLE RISK FACTORS (INFLUENCED BY SMOKING)

A. Electrocardiogram and Myocardial Status---------- 201
B. Hypertension---------- 204
C. Hypercholesterolemia--------- 207
D. Blood Coagulation---------- 214
E. Availability of Oxygen and Associated Changes in the Blood---------- 219

The preventable risk factors discussed in this section are those that are believed to be exaggerated by smoking. This supposition is based on observations of the effects of acute exposure to smoking in humans and animals and these are discussed in Section IX. The differences between habitual smokers and nonsmokers are described below. It should be stated at the outset that there is no concrete evidence for the hypothesis that chronic smokers show exaggerated electrocardiographic signs of ischemia, develop hypertension, hypercholesterolemia and hypercoagulation of the blood. The problem of reduced availability of oxygen in the blood of the habitual smoker is a complex one and is discussed under carbon monoxide (Section XI).

The general articles relating to the preventable risk factors are contained in the following Additional Bibliographic Lists:

List No. 19. Investigation of preventable risk factors in foreign countries.

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List No. 20. Ischemic changes in the electrocardiogram.
List No. 21. Hypertension as a risk factor.
List No. 22. Cholesterol and coronary heart disease.
List No. 23. Thrombosis induction and prevention.

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VIII-A. Electrocardiogram and Myocardial Status

The electrocardiogram has been used to assess the adequacy of oxygenation of the myocardium. The signs of ischemia in the electrocardiogram include depression of the S-T segment, inversion of the T wave and alteration in the QRS complex. These are useful in the diagnosis of coronary heart disease and in the detection of coronary-prone individuals (see Additional Bibliographic List No. 20).

The electrocardiogram of smokers, in contrast to that of nonsmokers, has been examined by several groups of investigators. Patients who develop chest pain during smoking show ischemic signs characteristic of tobacco angina (Boas and Levy, 1936; Wilson and Johnston, 1941; see also Section I-A). In patients prior to developing infarction as well as in those who have already developed it, there is a predominance of smokers over nonsmokers (Lafrenz, 1970; Iglesias Leal et al., 1971; Zdichynec and Prokš, 1971). This does not necessarily imply a cause and effect relationship because there are other risk factors which produce infarction.

The examination of the electrocardiogram of healthy smokers failed to show a significant difference in frequency of the ischemic pattern in the electrocardiogram as compared with that of nonsmokers (Agnese and Buonvino, 1964; Gelin et al., 1967; van Buchem, 1970; Hagerup, 1971). In similar surveys by other investigators, there were more smokers in the group that showed ischemic response in the electrocardiogram during exercise. Doyle and Kinch (1970) reported that 69% of subjects giving an

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ischemic response were smokers, whereas 37% of those with a normal electrocardiogram were smokers. Kattus et al. (1971) obtained the respective incidence of 59% and 42%. As in other studies, the role of various risk factors could not be excluded. When the heart was stressed by hypoxia, there was no difference between smokers and nonsmokers in the T-area vectors of the electrocardiogram (Abel, 1971). The QRS complex showed a right axis deviation in some smokers (Borden and Ibrahim, 1970). The polarcardiogram, which graphs the polar coordinates of the heart vectors vs. time, indicate a difference between smokers and nonsmokers (Dower et al., 1972). The complexity of the technique prevents its widespread application to determine the significance of the difference.

The heart of smokers in contrast to that of nonsmokers has been investigated by means of special techniques. The ballistocardiogram and other techniques for cardiac output measurement do not show any difference between smokers and nonsmokers in this respect (Starr (1954) and also Section IX-A).

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VIII-B. Hypertension

Hypertension is an important risk factor in coronary heart disease. The epidemiologic investigations of Pell (1961), Oberman et al. (1969) and Kannel et al. (1969, 1971) in the United States, of Tibblin (1967) in Sweden and of Kahn et al. (1972) in Israel demonstrate the major role of hypertension in the pathogenesis of coronary heart disease. There are other studies outlined in Table VII-E.

Essential hypertension as a separate disease entity has a set of precursors which include age, sex, familial, psychologic and dietary factors (Thomas, 1958; Lowenstein, 1961; Thomas et al., 1964; Paul and Ostfeld, 1965; Paul, 1971). Smoking is not one of them because smokers in the general population have a lower mean blood pressure than nonsmokers (Edwards et al., 1959; Borhani and Hechter, 1964; Clark et al., 1967). In groups preselected for absence of hypertension, there is no difference in mean blood pressure but a slight diminution in the response to the cold pressor test (Blackburn et al., 1960). A reduction of sympathetic vascular tone which occurs in smokers cannot be considered as contributing to a rise in blood pressure.

When essential hypertension appears together with coronary heart disease, the form of therapy indicated is to reduce the blood pressure by drugs (see Additional Bibliographic List No. 21). The influence of cigarette smoking in such a situation has not been investigated, since most studies relate either to essential hypertension of to coronary heart disease but not to both.

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VIII-C. Hypercholesterolemia

Hypercholesterolemia is one of the risk factors for coronary heart disease. In prospective studies, most patients who develop this disease also show an elevation of cholesterol and triglyceride levels in the blood serum (Kannel et al., 1971). Hypercholesterolemia is associated with other risk factors, including emotional stress, behavioral pattern and diet (Bronte-Stewart et al., 1955; Wertlake et al., 1958; Rosenman and Friedman, 1963; Rosenman et al., 1964; Jenkins et al., 1968; Pincherle, 1971). Therapy of coronary heart disease patient includes the use of diet and hypocholesterolemic drugs with the expectation that this would improve the prognosis in these cases (Cohen, 1969; Hughes, 1970; Coronary Drug Research Project, 1970; Newcastle-upon-Tyne Study Group (Dewar), 1971; Dayton, 1971; Dewar, 1972). The level of cholesterol drops following myocardial infarction per se, so that it is not reasonable to depend on this measurement to assess the severity and recovery from the infarction(Watson et al., 1963; Kurien and Oliver, 1966; Soloff and Schwartz, 1966).

The influence of cigarette smoking on the cholesterol level blood serum has not been completely settled. The results of 26 investigations are summarized in Table VIII-C. In half of these studies, smoking is associated with slight elevation of the cholesterol level, but in the other half there is no such elevation. When healthy subjects are matched according to their age group, body weight and behavioral pattern, there is no significant difference between smokers and nonsmokers (Schwartz et al., 1971).

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In patients with coronary heart disease, those who smoke have higher levels of cholesterol than nonsmokers and the arteriogram shows obstructive lesions more frequently in the former (Cramer et al., 1966). Smoking cannot be regarded as the cause of hypercholesterolemia and obstructive lesions, since other risk factors have not been excluded.

(Table VIII-C appears on the next two pages.)

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TABLE VIII-C.

Role of cigarette smoking in subjects with hypercholesterolemia

Country/Investigators	Subjects	Role of Cigarette Smoking
United States		
Gofman et al., 1955	123 healthy	Elevation of lipoproteins and cholesterol.
Burney and Enslein 1972	222 healthy	No difference in 5 year level of cholesterol compared to nonsmokers.
Spain and Nathan 1961	3,000 healthy males	Heavy smoking associated with higher cholesterol levels.
Talbott 1964	40 healthy males	Smoking while on a high fat diet suppressed rise in cholesterol and total artificial fatty acid.
Australia		
Mundy and Cutforth 1972	80 patients with myocardial infarction	Hyperlipoproteinenmia not associated with smoking.
Belgium		
Kornitzer et al., 1971	539 subjects	Hyperlipoproteinemia associated with coronary heart disease but not with smoking.
van Houte and Kesteloot 1972	42,804 males	Heavy smoking associated with higher cholesterol levels.
Finland		
Konttinen 1962	314 healthy young men	Smoking not related to cholesterol and phospholipids in serum.
Hernberg 1964	862 businessmen	Smoking not related to cholesterol level or capacity for physical work.
France		
Richard et al. 1969	7,672 subjects	Weak link between tobacco and cholesterol level and triglyceride
Lellouch and Beaumont 1967	1,053	Smoking not related to cholesterol level if body weight and age considered
Germany		
Gross [illegible], 1970	38 subjects	Smoking not related to cholesterol levels.
Great Britain		
Acheson and Jessop 1961	221 elderly men	Smoking not related with cholesterol or lipoprotein level.
McDonald et al., 1965	976 air force men	Smoking not related with cholesterol level.
Pincherle and Wright 1967	2,000 businessmen	Heavy smoking associated with higher cholesterol level.
Pozner and Billimoria 1970	64 young subjects	Heavy smoking associated with higher cholesterol and lipoprotein levels.
Pincherle 1971	7,000 businessmen	Heavy smoking associated with higher cholesterol level.
India		
Gupta 1964	286 subjects	Heavy smoking associated with higher cholesterol level.

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Italy		
Mattioli and Mancini 1959	51 subjects	Smoking not related to cholesterol level.
Balestra and Canepa 1967	47 normal and 36 patients	Smoking not related to cholesterol level.
New Zealand		
Smyth et al., 1970	70 patients with coronary heart disease	Smoking habit not reported
Norway		
Romslo 1971	324 military men	Smoking associated with higher triglyceride level.
Spain		
Portugal Alvarez et al., 1972	30 subjects with coronary heart disease	Smoking associated with high free fatty acid level.
Vlaicu et al., 1971	100 patients with coronary heart disease	Smoking associated with higher cholesterol level.
Sweden		
Carlson and Böttiger 1972	3,168 men	Elevated triglyceride and cholesterol observed for coronary heart disease but relation to smoking not reported
Switzerland		
Heyden-Stucky 1965	76 men with myocardial infarction	Smoking and hypercholesterolemia prevalent

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VIII. PREVENTABLE RISK FACTORS ALSO INFLUENCED BY SMOKING

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VIII-D. Blood Coagulation

The basic process of myocardial infarction consists of development of thrombosis in the atherosclerotic coronary artery. The process of blood coagulation has been investigated in such cases and measurements indicate hypercoagulability of the blood in patients with coronary heart disease (see Additional Bibliographic List No. 22).

Cigarette smoking has long been suspected of increasing coagulability of the blood. Most of the experiments have been carried out on animals and helathy subjects and the observations were made after a brief period of exposure to cigarette smoke (see Section IX-D). The present section pertains to differences between nonsmokers and smokers, which are as follows:

1. Coagulation time. Kedra and Korolko (1966) compared coagulation time in a group of 50 smokers and 50 nonsmokers. There were no significant differences in the various tests performed on the two groups. After the smokers consumed 5 cigarettes, there was a statistically significant shortening of clotting time, of plasma calcium time, and of factor V values, compared with the presmoking values. It is surprising to note that this is the only comparison between smokers and nonsmokers who are healthy. There is no comparison of subjects with coronary heart disease. Patients with ischemic heart disease show a decrease in coagulation time after smoking but there was no comparison with nonsmokers (Orlova, 1971). In an epidemiologic investigation of coronary heart disease, made in India,

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no relation was found between smoking habits, clotting time and incidence of coronary heart disease (Malhotra, 1968).

2. Fibrinogen level. In an examination of 788 men 54 years of age, smokers were found to have a higher fibrinogen level than nonsmokers (Korsan-Bengsten et al., 1972). In young adults, the fibrinogen level was not different as between smokers and nonsmokers (Ogston et al., 1970). The plasma fibrinogen level was not altered acutely by smoking one cigarette. The authors concluded that habitual use of cigarettes over a long period may induce hyperfibrinogenemia.

3. Fibrinolytic activity. The observations relating to fibrinolytic activity and smoking are limited to healthy subjects. Gibelli et al., (1964) reported a reduction in fibrinolytic activity in smokers. Loncin et al., (1968) reported that patients with coronary heart disease showed lower fibrinolytic activity than controls, but they did not investigate the influence of smoking.

4. Platelet aggregation. Although a considerable amount of work has been done to investigate the effect of smoking on platelet function, there is only one such study that can qualify as comparing smokers with nonsmokers. Hawkins (1972) examined three groups: nonsmokers, light smokers (using less than 1 pack a day) and heavy smokers. Changes in platelet activity could be separated into those apparent only after smoking and those detectable in the heavy smoker even after a nonsmoking period. The biphasic platelet electrophoretic mobility change was altered only after

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smoking and had returned to normal after 15 minutes. On the other hand, statiscally significant changes in thromboelastograph measurements were apparent in heavy smokers even during a nonsmoking period. Both acute and chronic changes seemed to result in an increase in platelet aggregation in the heavy smoker.

5. Influence of oral contraceptives. Frederiksen and Ravenholt (1970) suggested that the use of oral contraceptives and heavy cigarette smoking interact synergistically to increase the likelihood of thromboembolic disease. They reached this conclusion by a reanalysis of the data of Vessey and Doll (1968) who doubted that such an association existed. The interpretation by Vessey and Doll was supported by the previous study of Sartwell et al. (1969), in which there was no correlation between incidence of thromboembolism and the amount of cigarettes consumed. Sartwell (1971) has reexamined the literature and his own material and has concluded that, although there was some association of smoking with recent use of oral contraceptives, evidence was still lacking that smoking enhanced their effect in producing clotting.

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The interaction between contraceptives and cigarette smoking can be resolved by measuring the coagulability of blood. The effect of contraceptives on blood coagulation has been examined by Brakman et al. (1967) but these observations have not been extended to a comparison of smokers and nonsmokers. Patients who developed myocardial infarction in the course of using oral contraceptives have been examined thoroughly for the presence

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of risk factors by Oliver (1970) although he failed to measure blood coagulation. When these deficiencies are corrected, the potential hazard of combining smoking and the use of contraceptives will be more clearly defined.

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VIII-E. Availability of Oxygen and Associated Changes in the Blood

In recent years, there have been claims that the carbon monoxide contained in cigarette smoke reduces the availability of oxygen in the blood. The formation of carboxyhemoglobin and its consequences are discussed in Section XI.

There are other changes in the blood of smokers which differentiate them from nonsmokers. They are as follows:

1. Oxygen-dissociation curve. Aside from the formation of carboxyhemoglobin, there is a change in the affinity of hemoglobin for oxygen in the blood of smokers. This change is discussed in Section XI. Metcalfe et al. (1969) reported that patients with coronary heart disease and low output failure show a decreased affinity of the blood for oxygen. This is considered a compensatory adjustment to poor tissue blood flow, promoting the diffusion of oxygen from blood in tissue capillaries to intracellular sites of utilization. The status of this adjustment has not been examined in smokers who develop low output failure.

2. Hematocrit. There is an increase of the hematocrit in patients who develop acute myocardial infarction (Burch and De Pasquale, 1962; Stables et al., 1967). The resulting increase in the viscosity of the blood influences the free flow of blood and has been postulated to cause infarction (Dintenfass, 1969). This theory does not apply to smokers because there is no increase of the hematocrit in the blood.

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3. Blood cells. The distribution of blood groups is different between smokers and nonsmokers. With reference to white males, Cohen and Thomas (1962) reported that there appeared to be a significant deficiency of group B individuals among heavy smokers and an excess of group B persons among nonsmokers. There was also an excess of Rh negative individuals among the white occasional smokers. There were no significant differences among the Negro males. A genetic difference in blood groups has also been reported by Jick et al. (1969) in patients who develop coronary heart disease. The subsequent correspondence with Nefzger et al. (1969) and that with Havlik et al. (1969) indicate the problems in arriving at an unequivocal interpretation of prospective studies.

Another feature reported as appearing in smokers and patients with myocardial infarction is the occurrence of eosinophilia and lymphocytosis (Zdichyriec, 1971). This has been interpreted as an allergic response to tobacco but may also be a genetic response.

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PART FIVE

CIGARETTE SMOKING, NICOTINE AND CARBON MONOXIDE

IX. Acute Circulatory Effects of Cigarette Smoking.

X. Acute and Chronic Effects of Nicotine.

XI. Circulatory Effects of Carbon Monoxide.

In the preceding sections, the differences between smokers and nonsmokers have been discussed. The observations relating to the acute effects of smoking are considered in the present sections. These include not only the effects of cigarette smoke but also those of its constituents, namely, nicotine and carbon monoxide. The other chemicals present in cigarette smoke have been omitted, since hardly any report has been made of their action on the circulatory system.

The experimental observations discussed in these sections also include the chronic administration of smoke, nicotine and carbon monoxide to animals. The problem in these experiments is how to relate the results to smokers who develop coronary heart disease. Unfortunately, the amounts of nicotine and carbon monoxide administered to animals far exceed those which are absorbed during ordinary forms of smoking.

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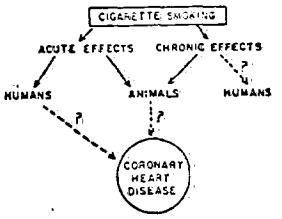
IX. ACUTE CIRCULATORY EFFECTS OF SMOKING



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D. Blood Coagulation---------- 250

To prove that smoking causes coronary heart disease, it is necessary to be able to reproduce the disease in the laboratory. So far, this has not been possible in animals. The animals subjected to chronic exposure to cigarette smoke have been few in number and the observations have been limited entirely to postmortem examination. Acute exposure has been performed largely on animals and humans without heart disease, so that it is difficult to relate the results to the disease state. Chronic exposure of humans to smoking is an impossible experiment because other risk factors are operative in habitual smokers.

The investigations of acute effects of smoking has been more significant in excluding rather than proving that it causes coronary heart disease. Smoking does not cause reduction of coronary blood flow, which is the primary hemodynamic defect in coronary heart disease. Smoking acutely increases blood pressure, whereas the habitual smoker is not hypertensive.

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Although patients with coronary heart disease show persistent elevation of the blood lipid level, habitual smokers do not necessarily experience this and smoking acutely does not consistently produce an elevation. Acute smoking increases blood coagulability in normal subjects and has not been thoroughly investigated in patients with coronary heart disease. The basis for these generalizations appears in the following sections. The Additional Bibliographic List relates to the reasons and manner of stopping the habitual use of cigarettes:

List No. 24. Cessation of cigarette smoking.

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IX. CARDIOVASCULAR EFFECTS OF SMOKING

Additional Bibliographic List No. 24

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IX-A. Cardiac Function

The influence of cigarette smoking on heart rate, cardiac output, stroke volume, myocardial contractility and metabolism is the primary concern of this section. However, each parameter will not be discussed separately but according to the manner in which it is derived. The technique of measuring cardiac output and the status of the subject, whether healthy or with coronary heart disease, are considered in the grouping. In investigations on animals, the acute are separated from the chronic.

1. Electrocardiogram. The most consistent effect of smoking in normal subjects is tachycardia (Grabiel et al., 1938; Buxtorf and Beaumont, 1968). The electrocardiogram of some patients with coronary heart disease shows inversion of the T wave and alteration of the QRS complex (Tobiasch, 1951; Kaltenback et al., 1967; Serafimova, 1971). The apexcardiogram (Aronow, 1971) and chronodynogram (Raab et al., 1960) have been applied and the results are similar to those of the electrocardiogram.

2. Ballistocardiogram. The early investigations on the effects of cigarette smoking involved the use of the ballistocardiogram (BCG) for the estimation of cardiac output (see Starr (1960, 1967) and Jackson et al., (1967)). The first application was reported by Henderson (1953), using subjects from the Hospital of the University of Pennsylvania. After smoking a single cigarette, the subject showed an increase in pulse rate but the form of the BCG remained normal in each of 50 healthy young adults. In 30 older persons believed to be healthy, there was a temporary abnormality of the

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ballistocardiogram in 4 instances. In 40 patients with coronary heart disease, the BCG became abnormal or more abnormal in form after smoking in 38% of these cases. No description was given of the smoking habits of subjects.

A group of 113 medical students, of whom 82 were smokers, were investigated by Thomas et al. (1956). A statistically significant change was noted in systolic, diastolic and pulse pressures, heart rate, stroke volume and cardiac output. There was no difference between smokers and nonsmokers. Among subgroups there were striking differences which were associated with family history. Subjects with parental hypertension, whose control cardiac output was large prior to smoking, showed more than twice as great an increase as did subjects with negative parents. Subjects with a parental history of coronary heart disease had very little increase in cardiac output in contrast to subjects with negative parents. In additional reports the investigators were able to reproduce their results (Thomas and Murphy, 1958, 1960a, 1960b).

The following investigations have confirmed most of the conclusions reported above: Levy et al. (1947) in 27 normal subjects and 21 patients with coronary heart disease; Russek et al. (1955) in 28 normal subjects and 37 patients; Davis et al. (1956) in 25 normal subjects and 190 patients with coronary heart disease; Dec (1960) in 15 normal subjects and 20 patients with myocardial infarction; Simon and Iglauer (1960, 1961) in 14 males without heart disease; Hanson (1962) in 3 patients with angina; Klensch (1963)

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in 39 subjects; Markewicz (1966) in 45 students; Buchanan (1969) in 19 young adults with coronary heart disease.

3. Dye Dilution Technique. The first application of a modern method for measuring cardiac output was accomplished by Irving and Yamamoto (1963). The smoking of one cigarette caused an increase in cardiac output in 15 normal subjects (Edmundowicz et al., 1964; Frankl et al., 1965). Pentecost and Shilingford (1964a, 1964b) compared subjects with patients. The healthy men and those with angina in the absence of infarction behaved similarly with an increase in cardiac output. However, some patients among the postinfarction group showed a marked fall in stroke volume and cardiac output while smoking.

Two procedures reduce the response of normal subjects to smoking. The previous administration of propranolol, a beta adrenergic blocker, decreased the intensity of cardiac output response (Frankl and Soloff, 1967). Pretreatment with glucose diminished the cardiac output response (Moses et al., 1964; Soloff and Powers, 1964). The explanation for the latter is not apparent but the influence of propranolol is related to its blockade of the cardiac effects of nicotine.

4. Coronary blood flow and myocardial metabolism. It has been supposed that cigarette smoking causes coronary spasm. This was disproven by catherization of the coronary sinus in man by Bargeron et al. (1957). Cigarette smoking in 30 normal subjects caused a significant rise in coronary blood flow, a decline in coronary vascular resistance and

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myocardial extraction of glucose and oxygen. In 7 males with myocardial infarction, smoking still caused an increase in blood pressure and heart rate. In 3 of the patients, coronary blood flow did not change, while in 3 others it fell slightly (Regan et al., 1960a, 1960b, 1961). Although there was slight increase in oxygen consumption in 3 cases, the myocardial efficiency was also increased. The data reported illustrate that in patients with coronary heart disease smoking results in no reduction of myocardial efficiency. In 15 patients with angiographically demonstrated severe obstructive coronary artery disease, cigarette smoking did not induce lactate production by the heart (Summers et al., 1971). There was no evidence of ischemia as determined by abnormalities in lactate extraction.

5. Exercise and the heart. Exercise has been used as a form of stress to detect borderline patients with coronary heart disease (Davis et al., 1953; Davis, 1959; Gusman and Khalfen, 1959). In subjects without clinical evidence of coronary heart disease, smoking does not interfere with their capacity to perform moderate exercise (see Section VII-A). There are observations which indicate that certain forms of exercise by particular individuals elicit responses which differ from the normal.

a. Exercise by bicycle ergometer severe enough to produce a fivefold increase in oxygen uptake of young male smokers caused an oxygen debt accumulation greater than that of nonsmokers. The oxygen debt of nonsmokers was 6.5% of the total increase in oxygen uptake, while for smokers it was 24.7% (Chevalier et al., 1963). In another group of subjects

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the same investigators (Krumholz et al., 1964) again reported an increase in oxygen debt but also a decrease in lung function, which were not noted previously. They also reported a decrease in diffusing capacity of the lung both at rest and with exercise. The exercise was more severe and reached up to 2 l/min, whereas in the first series it was 1.4 l/min. Since oxygen uptake is five- to sevenfold from a resting value of 0.3 l/min, this would be equivalent to running a race which is not ordinarily accomplished in the normal course of activity. It is necessary to measure oxygen uptake at various levels of exercise to determine the threshold for the increase in oxygen debt. The relation of activity to oxygen usage has been reviewed by Naughton (1967).

b. Smoking by patients with a healed myocardial infarction did not alter cardiac output significantly/ whether at rest or during exercise (Frankl et al., 1965a, 1965b). The lack of response in this group can be interpreted either way. The absence of an increase would mean that the infarcted heart has become tolerant to smoking. It can also mean that the heart has lost its capacity to respond, which is not valid since the subjects still showed an increase in output during exercise.

6. Canine heart. The dog has been the species most widely used in these investigations. In 1941, Bellet et al. studied dogs with chronic ligation of one coronary artery to simulate infarction occurring in man. Inhalation of cigarette smoke at 1/4 the dose administered prior to the infarction caused electrocardiographic changes. Thirty years later

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Bellet et al. (1972a) repeated the same experiments but measured the electrical threshold for ventricular fibrillation. After 30 minutes of exposure to smoke, the threshold to infarction was reduced. A similar effect was observed after administration of caffeine (Bellet et al., 1972b).

In an open-chest dog, the administration of cigarette smoke caused a brief decrease in oxygen utilization by the heart, but an increase in coronary blood flow (Kien et al., 1958; Kien and Sherrod, 1960). This coincided with the onset of irregularities which appeared early during the inhalation. This is different from the phenomenon reported by Bellet et al., which required 30 minutes for the reduction in the threshold to fibrillation to appear. The experiments reported by others on cigarette smoking in dogs confirm essentially the results in man, such as, tachycardia (Kaymakcalan et al., 1968), increase in coronary blood flow (Haft et al., 1966), and blockade of cardiac effects by propranolol (Edmundowicz et al., 1965; Westfall et al., 1966).

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Auerbach et al. (1967, 1971) and Hammond et al. (1970) have reported thickening of myocardial aterioles in beagles that have been exposed to cigarette smoke for several months. It is unfortunate that no measurements of cardiac function were made in animals prior to their being sacrificed. Reece and Ball (1972) subjected 7 dogs to exposure to cigarette smoke and treadmill exercise daily for one year. The electrocardiograms indicated enlargement of the heart. There was also thickening of the myocardial arterioles in 5 of the 7 dogs. However, no hemodynamic measurements were made

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similar to those completed in man.

7. Other animal species. Haag et al. (1960) exposed rats to cigarette smoke for their entire life span and they showed no significant differences in blood pressure, longevity and reproduction as compared with unexposed rats. No lesions were noted at autopsy. Myocardial lesions have been reported after chronic exposure to cigarette smoke in guinea pigs (Lupu and Velican, 1961, 1962) and mice (Komczynski, 1958). Ratcliffe (1965) examined coronary arteries of animals that died in the Philadelphia Zoological Garden during the period 1944 to 1964. The frequency of coronary arterial disease reflects the effects of physiological and psychological responses to social stimuli and environmental pollution. These animals were not exposed to cigarette smoke.

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IX-B. Blood Pressure and Peripheral Blood Flow

The early observations on the effect of tobacco smoke on blood pressure in man and animals have been summarized by Lee (1908). The response has been subsequently verified and standardized as the "smoking test" in humans (Thomas and Murphy, 1959; Kaufman et al., 1959; Roth and Shich, 1960). After the smoking of 1 cigarette, the rise in blood pressure, acceleration of heart rate and reduction of skin temperature are regarded as furnishing an assessment of the status of the lability of the circulatory system. An exaggerated response is interpreted as a sign of essential hypertension. This test, like the cold pressor test, is no longer widely used.

Among healthy subjects, the rise in blood pressure in response to cigarette smoking is greater and lasts longer in smokers than in nonsmokers (Keriigan et al., 1968). The hemodynamic cause of the rise in blood pressure is predominantly an increase in cardiac output rather than an increase in peripheral vascular resistance (Marshall et al., 1966, 1969; Goldberg et al., 1971; Krone et al., 1972; Wysonkinski, 1971). This conclusion is based on observations in normal subjects. Patients with angina pectoris after smoking and exertion also show a rise in blood pressure (Aronow and Swanson, 1969).

Although there is no increase in total vascular resistance following smoking, the blood vessels of the extremities show vasoconstriction. The following techniques have been applied: capillary circulation of the nail fold (Wright, 1933), hand plethysmograph (Lampson, 1935; Mulinos and

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Shulman, 1940; Shepherd, 1951), calf plethysmograph (Matsubara and Sano, 1972); cutaneous temperature (Moyer and Maddock, 1940; Roth and Shick, 1960; Furey et al., 1967), clearance of radioactive tracers in the extremity (Friedell, 1953; Coffman and Javett, 1963), direct microscopy of mucosa (Asano and Branemark, 1970) and electrical impedance (Allison and Roth, 1969). In patients with peripheral vascular disease the plethysmograph technique (Barnett and Boake, 1960) and the skin-temperature technique have been used extensively (Fleig, 1908; Hines, 1960; Wood, 1960, Freund and Ward, 1960; Zannini et al., 1963; Stallworth et al., 1967).

The vasoconstriction associated with cigarette smoking can be reduced in subjects who have been pretreated with reserpine (Westfall and Watts, 1961, 1962). The explanation is that depletion of catecholamnes by reserpine interferes with the primary action of nicotine (see Section X). The effect of smoking is vasodilatation in the cerebral (Kuhn, 1967; Miyazaki, 1969) and ophthalmic (Bettman et al., 1958) blood vessels. The reason for the lack of vasoconstriction in these areas is not known.

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IX-C. Blood Lipids

There are three lipids which are relevant in the consideration of the pathogenesis of atherosclerosis: Cholesterol, triglycerides and free fatty acids (Kershbaum and Bellet, 1966; Kershbaum, 1967; Mulcahy and Hickey, 1967; Boyle et al., 1968). The acute effects of smoking on the blood levels of these lipids are complex and varied. The smoking of 1 to 5 cigarettes has been reported by Göksel (1967) and Ciampolini et al. (1968) to increase the cholesterol level and by Butkus and Page (1965) and Page et al. (1959) not to influence it. For triglycerides, both an increase (Göksel, 1967) and no effect (Butkus and Page, 1965) have been reported.

The late Samuel Bellet and Alfred Kershbaum had investigated the effect of cigarette smoking on serum free fatty acids (FFA) in normal subjects. There was an elevation of FFA occurring 10 minutes after smoking cigarettes, and essentially no effect on serum cholesterol and triglycerides (Kershbaum et al., 1960, 1961). The increase of FFA in patients with healed myocardial infarct was greater than in normal subjects (Kershbaum et al., 1962). This increase is mediated through the adrenal glands and the sympathetic nervous system, because it was accompanied by an increase in urinary catecholamine excretion and the FFA response was blocked by sympathetic blocking drugs (Kershbaum et al., 1963; Kershbaum and Bellet, 1964). The thesis that they had developed was further elaborated by the following investigations: suppression of the free fatty acid response by ingestion of whiskey (Kershbaum et al., 1964), investigation of various

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forms of tobacco consumption in humans and dogs (Kershbaum et al., 1965, 1966; Kershbaum and Bellet, 1968; Kershbaum, 1968), and an increase in adrenocortical secretion accompanying the elevated FFA (Kershbaum et al., 1967a, 1967b; Kershbaum et al., 1968). Before Bellet died in 1971, he had completed the following sequence of conclusions as to how cigarette smoking causes elevation of the cholesterol level: (a) nicotine from tobacco releases catecholamines which mobilize FFA and lipoproteins; (b) in addition, catecholamines stimulate the anterior lobe of the pituitary gland to secrete adrenocorticotropic hormone (c) stimulation of the adrenal cortex releases hormones which play an essential and supportive role in the action of catecholamines on lipid metabolism.

The most important link in the above hypothesis is an increase in FFA following smoking. Several investigators have failed to observe an increase (Konttinen and Rajasalmi, 1963; Kedra et al., 1965; Frankl et al., 1966; Miturzyńska-Stryjecka et al., 1970). Furthermore smoking does not cause an elevation in blood sugar and epinephrinelike substances in the systemic blood (Rehder and Roth, 1959).

It has been difficult to obtain definitive proof that cigarette smoking causes an acute rise in blood lipids. Yet among habitual smokers there is an elevation in lipid levels as compared with nonsmokers (Harlan et al., 1967; Modzelewski and Malec, 1969; Tägert, 1970).

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IX-D. Blood Coagulation

Several investigations have been made in human subjects as to the fact that cigarette smoking causes an increase in coagulability of the blood (Murphy and Mustard, 1966). After smoking 1 to 10 cigarettes healthy young adults experience a shortening of clotting time and of thrombus formation time, and a decrease in fibrinolytic activity (Blackburn et al., 1959; Lisiewicz, 1963; Ambrus and Mink, 1964; Sogani and Joshi, 1965; Kedra and Korolko, 1965; Engelberg, 1965; Engelberg and Futterman, 1967; Engelberg and Engelberg, 1968; Schoendorf et al., 1970). It has been postulated by Engelberg (1965) that the hypercoagulability of blood is mediated by the release of epinephrine induced by nicotine. However, a proportionate dose response in the blood clotting system to the differing nicotine concentration could not be demonstrated by Schoendorf et al. (1970).

The acute effects of smoking on platelets include the following: no effect on total counts (Eisen and Hammond, 1956); shorter platelet survival time (Mustard and Murphy, 1963); increased platelet adhesiveness (Ashby et al., 1965; Engelberg and Futterman, 1966; Glynn et al., 1966; Murchison and Fyfe, 1966; El-Ebrashy et al., 1967; Facchini et al., 1971). None of the subjects had coronary heart disease or peripheral vascular disease. The relevance of these observations to patients with coronary heart disease can be determined only by investigation of such patients.

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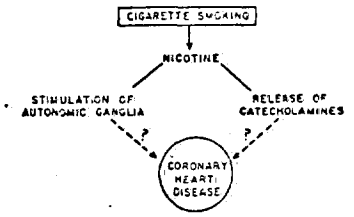
X. ACUTE AND CHRONIC EFFECTS OF NICOTINE



X NICOTINE

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D. Experimental Atherosclerosis- 277
E. Experimental Hyperlipidemias- 280
F. Experimental Thrombosis----- 282

The most important and widely investigated constituent of cigarette smoke is nicotine. The experimental use of this alkaloid has failed to produce coronary heart disease in animals that is similar to the human form. The pharmacologic action of nicotine can be attributed to stimulation of autonomic ganglia and the release of catcholamines. However, each mode of action taken singly has not been demonstrated to produce coronary insufficiency, experimental hypertension, atherosclerosis and thrombosis. Hyperlipidemia can be induced by catecholamines or nicotine but these same agents do not produce atherosclerosis unless the animal has also received a diet high in cholesterol.

The cardiac effects of nicotine do not in lude coronary vasoconstriction. However, it produces stimulation of the heart, which is potentially dangerous to a patient with coronary heart disease. The dose of nicotine used in the

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laboratory is so large that it is not yet possible to relate the cardiac effects to smoking by the patient with coronary heart disease.

The pharmacology of nicotine is discussed in the following Additional Bibliographic Lists:

List No. 25. Nicotine on isolated heart.
List No. 26. Release of catecholoamines from the heart.
List No. 27. Release of catecholamines from adrenal medulla.
List No. 28. Central nervous system effects of nicotine.

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X. CARDIOVASCULAR EFFECTS OF NICOTINE

Additional Bibliographic List No. 25

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X-A. Mode of Action on the Heart

The most important constituent of cigarette smoke that is responsible for its cardiac action is nicotine. The amount of nicotine absorbed in the respiratory tract ranges from 63 to 95%, depending on the duration of the period between inhalation and exhalation and the depth of the former (Larson, 1960). The percentage was derived by analyzing the content of nicotine in the smoke prior to and after the puff. The total amount of nicotine absorbed has also been estimated by analysis of urine for nicotine content (Beckett, 1967; Kershbaum et al., 1967; Cederlöf and Edfors, 1968). The mode of action of nicotine is as follows:

1. Nicotine effect on autonomic ganglia. Nicotine stimulates both groups of autonomic ganglia, the parasympathetic and the sympathetic. These ganglia are recorded as containing cholinergic fibers, a term introduced by Dale (1933) to indicate that acetylcholine is the chemical mediator. The result is either bradycardia from stimulation of parasympathetic ganglia, or tachycardia from stimulation of sympathetic ganglia (Aviado, 1972).

2. Release of catecholamines. The term nicotinic includes not only ganglionic stimulation (see above) but also the release of catecholamines in the adrenal medulla and in the area of adrenergic nerve endings in the heart (see Additional Bibliographic List No. 27). The release occurs not only following the administration of nicotine, but also following cigarette smoking (Westfall and Watts, 1963; Klensch, 1966; Klensch et al., 1967; Schievelbein and Werle, 1967). The end result is stimulation of the heart similar to the

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effect of epinephrine and norepinephrine (Lickint, 1959; Robin et al., 1969).

3. Neuropharmacological and biochemical effects. Nicotine, like epinephrine, increases the excitability of the heart (Frommel, 1928). There is also an increase in duration of the action potential of isolated rat atrial muscle unrelated to changes in rate and contractility (Shibata et al., 1968). In the dog ventricle a defect in conduction occurs and appearance of fibrillation following the injection of nicotine or inhalation of cigarette smoke (Webb, 1968; Greenspan et al., 1969). There are changes in myocardial metabolism and lysosomal enzymes resulting from the addition of a toxic dose of nicotine (Brachfeld and Oran, 1966; Brachfeld et al., 1967). The dose used is not normally encountered in ordinary smoking.

4. Cardiac necrosis. Large doses of nicotine administered in conjunction with isoproterenol cause necrosis of the rat heart (Wenzel et al., 1964; Wenzel and Stark, 1965, 1966; Wenzel, 1967). The interaction between isoproterenol and nicotine is attributable to the release of catecholamines by the latter. Several adrenergic blocking drugs are available and they have not been applied to the investigation of how nicotine produces cardiac necrosis (Papp and Solti, 1959; Papacostas and Reed, 1966; Shanks, 1966).

5. Chemoreceptors and chemoreflexes. The administration of large doses of nicotine brings about a stimulation of chemoreceptors in the carotid and aortic bodies (Stern et al., 1964; Hashimoto et al., 1964; Stern and Rapaport, 1967). The epicardial surface of the heart contains receptors which are activated by topical administration of nicotine (Sleight, 1964; Bergel and

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Makin, 1966, 1967). The responses to stimulation of chemoreflexes in the heart and the chemoreceptors in the carotid and aortic bodies are variable and include tachycardia or bradycardia and coronary vasoconstriction or vasodilatation. In the pulmonary circulation, the response to nicotine is the outcome of stimulation of chemoreflexes and release of catecholamines (Larson and Murray, 1963; Stern and Braun, 1966; Samaněk and Aviado, 1966). It has also been demonstrated that smoke inhalation in the dog causes the release of histamine which may in turn influence the heart (Aviado et al., 1966).

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X-B. Experimental Coronary Insufficiency

The early experiments showed that nicotine causes coronary vasoconstriction in the perfused isolated heart (Laubry et al., 1933; Wegria, 1951). In the dog coronary vasoconstriction could not be elicited by nicotine injected directly into the coronary artery of an intact heart (West et al., 1958, 1962; Bellet et al., 1960a), intravenously in the intact animal (Kien et al., 1957; Forte et al., 1960), or in the perfused canine heart (Leaders and Long, 1962), and in the heart-lung preparation (Folle et al., 1966).

Bing and his collaborators have systematically examined the effects of nicotine on the coronary circulation. Their experiments relating to the acute effects of cigarette smoking on the human heart are discussed in Section IX-B. In the animal heart, they measured capillary blood by means of radioactive iodinated albumin. Nicotine did not influence coronary capillary blood flow in the dog heart, unless the dose was large enough to influence blood pressure (Rakuson et al., 1968; Rival and Mathes, 1969). By means of radioactive Rubidium for estimating effective coronary flow, Leb et al. (1970) noted that after nicotine injection there was a significant correlation between supply of oxygen (effective blood flow) and oxygen demand of the myocardium. By direct visualization of the coronary capillaries, an increase was noted in the movement of red blood cells on the surface of the cat heart following the injection of nicotine (Bing et al., 1971; Hellberg et al., 1972; Pachinger et al., 1972). There is no evidence that nicotine causes coronary insufficiency in the normal heart.

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In some investigations performed on the dog heart with ischemia, Bellet et al. (1960b) observed that the increase in coronary blood flow in response to nicotine was considerably less in the ischemic heart as compared with the normal heart. A reduction in capillary blood flow of the ischemic heart following nicotine injection has been observed by Corsini et al. (1968) and Mathes and Rival (1971). A reduction in response to nicotine has also been observed in the atherosclerotic rabbit heart (Travell et al., 1960) and in the heart with pitressin-induced spasm (Kareva, 1963). The avian hearts show only a vasoconstrictor response to epinephrine, whereas the hearts of other species show a vasodilation (Juhasz-Nagy et al., 1965).

The increase in coronary blood flow following nicotine injection is accompanied by an increase in cardiac output in the dog (Corbascio and West, 1960; Larson et al., 1965). This effect is the outcome of positive chronotropic (Nadeau and James, 1967; Ross and Blesa, 1970) and positive inotropic action of nicotine (Puri et al., 1967, 1968). The phenomenon occurs also in man following the injection of nicotine (Boyle et al., 1947; Schweizer et al., 1960; Dock, 1963; Valori et al., 1964; Solti et al., 1964).

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X-C. Experimental Hypertension

Nicotine causes vasoconstriction of the extremities. This effect has been demonstrated in normal subjects following injection of nicotine into the brachial artery (Stromblad, 1959; Whelan,, 1968) or after it has been injected intravenously (Rottenstein et al., 1960; Solti et al., 1966). Vasoconstriction in response to nicotine has also been noted in the bat wing (Martz et al., 1970) and in the mesenteric vessels of the cat (Saphir and Rapaport, 1969) and of the rat (Balourdas, 1966; Albertini et al., 1967). There was no reduction in blood flow in rat skeletal muscle (Rakusan, 1967) and human brain vessels (Solti et al., 1963).

Several attempts have been made to develop hypertension in animals receiving nicotine for an extended period of time. Wenzel et al. (1964) treated rats for 55 weeks and observed first an elevation and then a depression of systolic pressure. Ahtee and Mattila (1966) failed to produce chronic hypertension. The only successful attempt is that of Bhagat (1968). Individuals who are habitual smokers have a lower mean blood pressure than nonsmokers (see Section IX-B). A possible explanation has been suggested by observations of Bhagat et al. (1971) that in dogs nicotine causes vasodilation by a central action and by stimulation of beta adrenergic receptors through the catecholamines released during exposure to cigarette smoke.

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X-D. Experimental Atherosclerosis

In the course of investigating the toxicity of nicotine, Adler and Hensel (1906) discovered lesions in the aorta of rabbits. The lesions were degenerative and aneurysmal; they were similar to those induced by epinephrine and unlike the human form of atherosclerosis. Degenerative lesions were later seen in rabbits by Grosgogeat and Roubelakis (1965) and Lellouch et al. (1968) and in dogs by Hueper (1943) but were not seen in rats by Thienes (1960). The chronic administration of nicotine alone caused a transient increase in blood lipids but the level approximated the control level towards the end of the experiment (Schivelbein et al., 1970). Although the calcium controls of the aorta of nicotine-treated rabbits was increased, there were no differences in histological changes in the blood vessels between nicotine-treated and control rabbits.

The rabbit has been the favorite animal for experimental induction of atherosclerosis. The initial attempt of Wenzel et al. (1959) failed to establish an increase in severity of atherosclerosis in rabbits on a high cholesterol diet. Two other groups reported an increase in extent of dietary-induced atherosclerosis in nicotine-treated rabbits—one group from Chicago (Haas et al., 1966a, 1966b, 1968; Landerholm et al., 1967) and another group from Boston (Stefanovich et al., 1969). The oxygen uptake of tissues from hypercholesterolemic rabbits has been reported to be more sensitive to the depressant action of nicotine than that of tissues from

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normocholesterolemic rabbits (Adachi et al., 1965). Nicotine was shown to change the lipid patterns of the perfused dog aorta and coronary artery (Kupke, 1972). The results were regarded by the author as supporting the hypothesis that nicotine may impair oxidative enzymes by damaging the mitochondrial structures, thereby leading to lipid accumulation. Experiments on the atherosclerotic dog aorta and the human aorta are needed.

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X-E. Experimental Hyperlipidemias

Epinephrine is known to mobilize free fatty acids from fatty tissue and this was followed by elevation of cholesterol and triglycerides in the blood (Kaplan et al., 1957; Sussman et al., 1958). A similar response was noted to nicotine administration in dogs (White et al., 1964; Kershbaum et al., 1965, 1967a, 1967b). There is also an accompanying elevation of blood glucose related to the release of epinephrine which has a glycogenolytic action (Tsujimoto et al., 1965; Milton, 1966). Hyperlipidemia induced in dogs by nicotine can be prevented by prior injection of adrenergic blocking drugs (Kershbaum et al., 1966). Animals with hypercholesterolemia show an interaction with nicotine. The administration of nicotine and ergonovine produces necrosis in the heart (Wenzel et al., 1961). Grosgogeat did not find lesions in the rabbit aortic wall with nicotine treatment alone (Grosgogeat et al., 1965). There is a diminution in the rate of synthesis of cholesterol in dogs that have been subjected to chronic administration of nicotine (Gudbjarnason, 1968). The relationship of cholesterol to atherosclerotic lesions is discussed in the preceding section.

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X-F. Experimental Thrombosis

The release of epinephrine from the adrenal medulla has been known to increase the coagulability of the blood in vitro (Cannon and Gray, 1914; Cannon and Mendenhall, 1914a, 1914b). More recently, this phenomenon regarding epinephrine has been demonstrated by techniques involving experimental thrombosis (Rosewell et al., 1966) and platelet aggregation (Shimamoto and Ishioka, 1963; Ardlie et al., 1966; Hampton and Mitchell, 1966; Besterman et al., 1967).

That nicotine releases epinephrine does not necessarily mean that all its reported effects on blood coagulation are mediated through this mechanism. Platelet aggregation results from the in vitro addition of nicotine, which must act directly on the cells not containing a significant amount of epinephrine (Werle and Schievelbein, 1965). In the rat, the thrombosis induced by a single subcutaneous injection of carragenine and nicotine can be simulated by substituting epinephrine for the nicotine (Jan et al., 1969). Chronic injection of nicotine in the same animal species caused decreased thrombus formation, indicating that there is no experimental support for the statement that habitual smokers are susceptible to thrombus formation (Wenzel and Richards, 1970). In rats maintained on a hypercholesterolemic diet, the administration of nicotine shortens coagulation time (Singh, 1965).

In other species, nicotine has varied effects, such as: reduction of toxicity of nicotine injected intravenously by increasing the number of platelets by transfusion in rabbit (Schievelbein and Schirren, 1964), decrease of

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fibrinolysin in the guinea pig by chronic administration of nicotine (Belli et al., 1965), and nicotine-heparin antagonism when added to human blood in vitro (Singh and Oester, 1964a, 1964b). These observations suggest that nicotine influences coagulability by several mechanisms other than the release of epinephrine.

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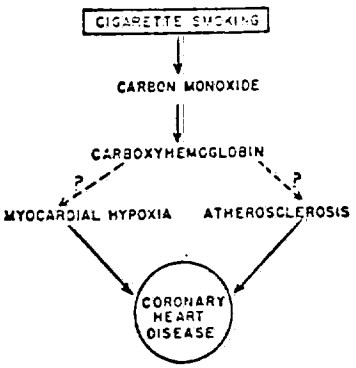
XI. CIRCULATORY EFFECTS OF CARBON MONOXIDE



XI CARBON MONOXIDE

A. Carboxyhemoglobin Blood Levels---------- 287
B. Influence of Smoking on Alveolar Air and Blood Levels of Carboxyhemoglobin-------- 295
C. Coronary Circulation and Myocardium---------- 300
D. Experimental Atherosclerosis-- 308
E. Blood Cells and Plasma-------- 315

The most important single measurement for assessing the extent of exposure to carbon monoxide contained in cigarette smoke is that of the blood level of carboxyhemoglobin. This form of hemoglobin reduces the availability of oxygen, so that there is a danger of producing generalized hypoxia. It has been suggested that the hypoxia in the myocardium would lead to coronary heart disease and vascular hypoxia to atherosclerosis. The experiments which form the basis of this statement are analyzed in the present section.

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The author has completed a separate review entitled "Cigarette Smoking and Carbon Monoxide" and submitted it to the Council for Tobacco Research on January 3, 1973. It contains a discussion of the effects of carbon monoxide as it relates to cigarette smoking. The circulatory effects are recounted in this section and the literature has been updated to July 1, 1973.

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XI-A. Carboxyhemoglobin Blood Levels

The carboxyhemoglobin present in the blood is not able to dissociate readily to allow the hemoglobin portion to combine with oxygen. The blood levels are reported for the habitual smoker compared with the nonsmoker, and the acute elevation during cigarette smoking.

1. Habitual smokers compared with nonsmokers. The first identification of carboxyhemoglobin in blood of smokers was accomplished by Hartridge (1919-1920). He estimated the carboxyhemoglobin level in one smoker to be 6% and in another to be absent. A more extensive investigation was completed by Gettler and Mattice (1933), who compared four groups of habitual cigarette smokers. The group of 12 rural dwellers had a mean value of 1.2% carboxyhemoglobin in the blood, while 18 New York City residents had a mean of 1.4%, 12 New York City cleaners a mean of 3.5%, and two New York City taxi drivers a mean of 13.5%. These results proved for the first time that the carboxyhemoglobin contained in blood of habitual smokers was not only the result of cigarette smoking but was also the outcome of inhaling an atmosphere containg carbon monoxide released from automobile exhaust and other sources.

There have been 28 additional reports of carboxyhemoglobin in blood levels among cigarette smokers and the results are summarized in Table XI-A. The mean values do not represent the effect of cigarette smoking because the contribution of carbon monoxide in the atmosphere has to be subtracted. The last column in Table XI-A is the net level of carboxyhemoglobin which can be attributed to cigarette smoking and was obtained by subtracting the mean

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blood levels for controls who were nonsmokers. The following generalizations can be made from the published results.

a. The 30 investigations summarized in Table XI-A were performed in various cities in the United States and Europe. The highest mean level is 16.2% for a group of 6 U.S. Army enlisted men (Meigs, 1948). This represents an error in the analysis, since the blood levels for nonsmokers were also high. All the other mean levels were below 10% carboxyhemoglobin.

b. The overall mean level for 2,054 subjects reported in the 30 investigations is 3.76%. This represents the average blood level for smokers in the morning, 4 to 12 hours after they smoked a cigarette.

c. The contribution of atmospheric pollution to the increased blood levels of carboxyhemoglobin can be derived by subtracting the blood levels for controls who were nonsmokers. Twenty-one of the investigations included nonsmokers, so that it was possible to subtract their mean levels from those of habitual smokers. The net difference between 2 groups represents the contribution from smoking alone, which amounted to a mean of +2.19% of carboxyhemoglobin for 2,781 subjects. This mean value was calculated regardless of the number of cigarettes consumed.

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d. Ten investigators related the amount of cigarettes consumed daily to blood levels of carboxyhemoglobin. The consumption of 20 or less cigarettes per day showed the following net change in blood carboxyhemoglobin levels in each case: +1.6% (Schmidt, 1939); +2.4% (Schrenk, 1942); +2.1% (Parmeggiani and Gilardi, 1952); +1.0% (Goldsmith et al., 1963); +1.9%

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(Curphey et al., 1965) +0.3% (Balbo et al., 1966); and +0.9% (Rouch et al., 1971). The net changes in blood carboxyhemoglobin levels for subjects consuming one or more cigarettes were respectively: +2.9% (Schmidt, 1939); +3.7% (Schrenk, 1942); +3.5% (Parmeggiani and Gilardi, 1952); +1.1% (Goldsmith et al., 1963); +3.6% (Curphey et al., 1965); +2.0% (Balbo et al., 1966); and +8.0 (Yacoub et al., 1970). The last-mentioned value represents the highest net level of carboxyhemoglobin, next to the +11.0% referred to above as reported for the U.S. Army enlisted men.

(Table XI-A appears on the next page.)

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Table XI-A. Carboxyhemoglobin levels in the blood of habitual smokers.[1]

Reference (Year)	Nature of habitual smokers (Cigarette consumption)	No. of Subjects	Carboxyhemoglobin blood level %: Smokers Mean ± SD (Range)		Non-smokers Mean	Net
Hartridge (1919-1920)	London volunteers	2	3.0	(0-6)		
Gettler and Mattice (1933)	New York residents	18	1.4	(1.0-4.1)		
	New York street cleaners	12	3.5	(1.2-0.9)		
	New York taxi drivers	2	13.5	(8.0-19)		
	Rural dwellers	12	1.2	(0.5-3.6)		
Ruhl and Lin (1936)	Berlin volunteers					
	(non-inhalers in morning)	21	0.6			
	(inhalers in morning)	25	0.5			
	(heavy inhalers in morning)	13	1.3			
	(heavy inhalers in evening)	13	2.6			
Schmidt (1939; 1940)	Bonn volunteers					
	(20-30/day)	3	3.5		0.6	+2.9
	(>30/day)		7.2			+6.6
	(10-20/day)		2.2			+1.6
	(<10/day)		1.5			+0.9
Schrenk (1942); Sievers, Edwards Murray and Schrenk (1942)	Holland tunnel workders					
	(<20/day	39	4.1 ± 1.9		1.7	+2.4
	(>20/day)	21	5.4 ± 1.8			+3.7
	(pipe)	5	2.5			
	(cigar)		3.2			
Wennesland 1945	Stockholm volunteers					
	(<15/day)	35		(0.5-10.5)		
	(pipe)	7		(0-11.5)		
Meigs 1948	US army enlisted men					
	(6-20/day	6	16.2	(1.9-45)	5.2	+11.0
Parmeggiani and Gilardi (1952)	Italian volunteers					
	(10-12/day)	14	4.9	(1-9)	2.8	+2.1
	(15-25/day)	6	6.3	(2-9.5)		+3.5
	(30-40/day)	3	9.3	(6-14)		+6.5
Barthe, Paris, Duchemin and Thomas (1953)	Paris workers	100		(0.8-2.0)		
Ruel and Barthe (1954)	Paris workers					
	(<10/day)		1.0			
	(10-15/day)		1.7			
	(>20/day)		2.7			
Valic and Duric (1954)	Yugoslavian workers	75	3.8 ± 1.9		0.9	+2.9
Gettler, Cadigan, Wilcott, Jones and Marks (1957)	Boston workers	9	4.7	(3.1-7.9)	0.9	+3.8
Dahlström, Nordström-Öhrberg and Rothschild (1958)	Stockholm volunteers	6	2.1	(1.2-3.0)	0.7	+1.4

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Reference (Year)	Nature of habitual smokers (Cigarette consumption)	No. of Subjects	Carboxyhemoglobin blood level % Smokers Mean ± SD (Range)	Non-smokers Mean	N
[illegible]nder and Harper (1962)	Sunderland volunteers	3	3.8 (3.2-4.8)	0.9	+2.9
Hofreuter, Catcott and Xintaras (1962)	Cincinnati volunteers	19	2.9	1.9	+1.0
Goldsmith, Schuette and Novick (1963)	San Francisco longshoremen				
	(<10/day)	429	2.3	1.3	+1.0
	(10-40/day)	1035	3.4		+1.1
	(>40/day)	233	5.5		+4.2
Curphrey, Hood and Perkins (1965)	Los Angeles longshoremen				
	(light)	55	2.3	0.4	+1.9
	(medium)	153	3.0		+2.6
	(heavy)	29	4.0		+3.6
Ayres, Gianelli and Armstrong (1965)	New York volunteers	25	4.2	0.9	+3.3
	[illegible]				
Balbo, Marucci and Ronchi (1966)	Paris workers				
	(5/day)	34	2.1 (0-9.8)	1.9	+0.2
	(10/day)	32	2.2 (0-9.5)		+0.3
	(15/day)	16	2.2 (0-5.9)		+0.3
	(20/day)	20	2.2 (0-6.9)		+0.3
	(30/day)	7	2.8 (0-5.2)		+2.0
[illegible]avaine, Nelson and Bartlett (1969)	Durham workders	5	3.8	1.6	+2.2
Bhown, Maitrya and Haq (1969)	Indian beedi smokers				
	(<10/day	7	4.8 (3.4-5.6)		
	(10-19/day)	8	5.9 (5.6-6.1)		
	(20-29/day)	8	6.9 (6.6-7.3)		
	(>29/day)	7	9.4 (8.5-10.5)		
Yacoub, Faure, Mallion and Cau (1970)	Paris workers				
	(20/day inhaled)	90	9.5	1.5	+8.0
	(20/day non-inhaled)	97	6.0		+4.5
Rouch, Rioufol and Bourbon (1971)	Toulouse volunteers				
	(<10/day)	5	2.5 (1.0-5.5	1.6	+0.9
	(>10/day)	15	4.25 (1.0-11.0)		+2.6
Brewer, Eaton, Weil and Grover (1970); Brewer, Eaton, Grover and Weil (1971)	Leadville volunteers	20	6.6 ± 2.7		
Weiss, Slawsky and Desforges (1971)	Boston patients with fibrosis	8	4.2 ± 2.7	1.5	+4.2
[illegible]y (1971)	Los Angeles residents	81	5.7 (3.2-14.2)	1.5	+4.2
Hansen, Wilke, Malorny and Gothert (1972)	Hamburg workers	40	4.9 ± 1.0	0.75	+4.2

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Reference (Year)	Nature of habitual smokers Cigarette consumption)	No. of Subjects	Carboxyhemoglobin blood level % Smokers Mean ± SD (Range)		Non-smokers[2] Net Mean	
[illegible]rson, Garby, [illegible]bert and Zaar (1972)	Uppsala volunteers	6	2.7	(1.5-4.4)	1.27	+1.4
Mean (overall for number of subjects)			3.76 (2954 subjects)			+2.19 (2781 subjec

[1] Some of the values were reported in volumes % and are expressed in this table as saturation % assuming normal hemoglobin values.

[2] See Table 4 for details.

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XI-B. Influence of Smoking on Alveolar Air and Blood Levels of Carboxyhemoglobin

Jongbloed (1939) analyzed the carbon-monoxide content in alveolar air. A trace of carbon monoxide (about 0.0004% or 4 ppm) was detectable in the alveolar air of nonsmokers. In one smoker the content was 10 ppm in the morning before smoking. Then the subject was given 4 cigarettes, each one taking 12 min to smoke with an intervening 12-minute rest period. The results were as follows:

before 1st cigarette	14.0 ppm
after " "	17.9 "
before 2nd "	19.4 "
after " "	23.2 "
after 3rd "	27.1 "
after 4th "	31.5 "
32 min after 4th cigarette	29.0 "
52 min " " "	26.6 "
72 min " " "	23.7 "

There was a progressive increase in the level of carbon monoxide in the alveolar air up to the end of smoking the 4th cigarette. Then a fall occurred in the concentration of carbon monoxide in the alveolar air.

Other investigators have confirmed the observation of Jongbloed. Ringold et al. (1962) analyzed the expired air after a 20-second breath-holding period. The mean ± SD levels of carbon monoxide were as follows:

Nonsmokers (93 subjects)	0.8 ± 4.7 ppm
Heavy smokers (41 subjects)	16.4 ± 12.6 "
Light smokers (25 subjects)	7.7 ± 10.9 "
Pipe or cigar (9 subjects)	3.8 ± 4.9 "

Cohen et al. (1971) reported similar observations and correlated expired air levels of carbon monoxide with blood levels of carboxyhemoglobin.

The results of investigations relating to blood carboxyhemoglobin

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levels are summarized in Table XI-B. The essential features of the table are:

1. The 11 investigations consisting of measurements of carboxyhemoglobin in blood, resulted in a mean peak level of 5.26% in 29 pooled subjects. The net effect of smoking which was calculated in 15 subjects was an increase of 3.81% of carboxyhemoglobin.

2. There are isolated values as high as 12.3% (Farach et al, 1941), 10% (Ruhl and Lin, 1936) and 6.5% (Whitehead and Worthington, 1961). However, since the control value prior to smoking was not measured, it was not possible to calculate the net effect of smoking.

3. None of the investigations summarized in Table XI-B determined the duration of the rise in carboxyhemoglobin. On the basis of work concerning experimental inhalation of carbon monoxide mixture, the duration depends on the concentration of inspired air. There is probably a slow fall in carboxyhemoglobin until the next cigarette is smoked.

After cessation of smoking, a reduction occurs in blood levels of carboxyhemoglobin (Belli and Guiliani, 1955; Ramsey, 1972; Rosenberg, 1968, 1971, 1972). The rate of fall in concentration was accelerated by exercise or muscular effort (Castellino, 1955; Crosetti et al, 1966; Shields, 1971).

Animals have been exposed to cigarette smoke for the investigation of its effect. The blood level of carboxyhemoglobin is elevated in mice (Leuchtenberger et al, 1965), hamsters (Dontenwill et al, 1966, 1967) and rats (Driscoll et al, 1972). In the last-mentioned species, the blood level of carboxyhemoglobin was influenced by the nature of cigarette used. With unfiltered smoke, the rat held its breath, whereas filtered smoke was inhaled with continuation of thoracic respiration.

(Table XI-B appears on the next page.)

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Table XI-B. Acute effects of cigarette smoking on carboxyhemoglobin levels.[1]

Reference (Year)	Number of Cigarettes	No of Subjects	Peak Carboxyhemoglobin blood levels: Mean	(Range)	Δ
Eason and Hastings (1933)	10-15	6	4.3	(3.1-6.7)	
Ruhl and Lin (1936)	1-2	5		(3.2-10)	
Schmidt (1939, 1940)	1	1			+1.1
	5	2			+1.6; +4
Hsi-Pu and LiMing (1940)	1-5	43	(<5 in 80% of subjects)		
Barach, Eckman and Molomut (1941)	20	18	5.7	(2.2-12.3)	
MacFarland, Roughton, Halperin and Niven (1944)	1	1			+2.0
	3	1			+4.0
Fabre, Truhaut and Berrod (1951)	24	5	4.85		+2.7
Parmeggiani and Gilardi (1952)	2	1			+3
Osmith, Terzaghi and Hackney (1963)	12	1			+11.9
Bowden and Woodhall (1964)	2	2			+1.5
Hamill and O'Neill (1969)	20 (cigars)	1			+13
Mean (overall for number of subjects)		5.26 (29 subjects)			+38 (15 subjects)

[1] Some of the values were reported in volumes % and are expressed in this table as saturation % assuming normal hemoglobin values.

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XI-C. Coronary Circulation and Myocardium

In recent years there has been an increasing number of publications associating coronary heart disease with the carbon monoxide contained in cigarette smoke (Jaffe, 1968; Dinman, 1969; Robin et al., 1969; Goldsmith, 1970; Szollosi et al., 1970; Tibblin, 1971; Schievelbein and Eberhardt, 1972; Maryland and Bersay, 1972). The evidence for stating that the carbon monoxide content of cigarette smoke causes coronary heart disease is indirect. A review of the investigations concerned reveals that the levels of carboxyhemoglobin in the blood of habitual smokers are unlikely to cause coronary heart disease.

1. Coronary circulation. The effect of exposure to lower concentrations of carbon monoxide in high-pollution areas of Los Angeles has been examined by Cohen et al. (1969). The case fatality rates for patients admitted with myocardial infarction to 35 hospitals during 1958 were examined. The results indicate that there was an increase in fatility rate in high-pollution areas and that this difference was evident during periods of relatively increased carbon monoxide pollution. However, it was not possible to prove cause and effect relationship between carbon monoxide and high fatality rate, since there are other pollutants involved. In the same city, Haywood et al. (1972) examined 34 patients with acute myocardial infarction and 35 control patients with diverse diseases. Carboxyhemoglobin levels averaged 5.14% for the infarct patients and 4.8% for the controls; there was no clear-cut relationship between carbon monoxide and acute infarction. For patients with angina pectoris, exposure to the heavy morning freeway traffic in Los Angeles

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caused a decrease in exercise performance that initiated the onset of angina (Aronow et al., 1972). The mean blood levels of carboxyhemoglobin in % were 1.12 ± 1.20 before, 5.08 ± 1.19 immediately after leaving the freeway, and 2.91 ± 0.93 two hours later. Any one of the pollutants other than carbon monoxide may be responsible for quicker development of angina after less cardiac work. Ten patients with angina pectoris were examined by Aronow and Rokaw (1971) and Aronow et al. (1971) following the smoking of low-nicotine cigarettes. After each subject had smoked 8 cigarettes, at the rate of one every 30 min, the carboxyhemoglobin level in the blood rose from 1.58 to 7.79%. This was accompanied by a decrease in exercise tolerance. The only direct proof would be to repeat similar observations on patients inhaling carbon monoxide mixture. De Bias et al. (1972) exposed dogs with myocardial infarction to 100 ppm carbon monoxide for 14 weeks. The elevation of the blood carboxyhemoglobin level to 14% did not influence the electrocardiogram nor the serum enzymes that would be expected to accompany increasing severity of hypoxia. Carbon monoxide alone, producing up to 14% saturation of carboxyhemoglobin, does not appear to exaggerate myocardial infarction in dogs. Exposure of rabbits for up to 14 months, resulting in a blood level of 15 to 40% carboxyhemoglobin, causes myocardial damage (Andersson, 1972).

The effects of inhalation of 0.1 or 5% carbon monoxide, sufficient to raise the carboxyhemoglobin level to between 5 and 25% in dogs and humans, were reported by Ayres et al. (1969, 1970). There was an increase in coronary blood flow and alteration of lactate and pyruvate metabolism. Most of these changes would be accounted for by hypoxemia, although a direct effect of

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carbon monoxide on the coronary vessels has not been excluded. One of the five subjects that inhaled 0.14% carbon monoxide developed evidence of mild left-ventricular dysfunction (Ayres et al., 1965).

2. Cardiac output. Exposure to carbon monoxide resulting in carboxyhemoglobin levels of 10% saturation does not influence cardiac output in subjects after a few hours (Brody and Coburn, 1969, 1970) or after 8 days (Klausen et al. 1968). With levels exceeding 15% saturation, there is either an increase or a decrease in cardiac output (Diamant-Berger et al., 1970; Katzschmann, 1970).

The response of the heart to muscular exercise has been assessed during exposure to carbon monoxide. Guillern et al. (1907) exposed 12 subjects to a concentration of 50 to 100 ppm and noted an increase of cardiac acceleration during effort. Chevalier et al. (1963) previously reported a lower heart rate for exercising subjects exposed to carbon monoxide, but the concentration was not stated. Pirnay et al. (1971a and b) reported cardiac acceleration due to muscular exercise during exposure, with carboxyhemoglobin saturation of 15%, but no comparison was made with exercising subjects not submitting to carbon monoxide inhalation. Vogel and Gleser (1972) and Vogel et al. (1972) investigated blood levels as high as 20% saturation and failed to show a difference in cardiac output response, although there was an exaggerated tachycardia during exercise as compared with subjects not experiencing hypoxia. The pumping capacity of the heart is not influenced by carboxyhemoglobin blood levels of up to 20%. Krumholz et al., (1964, 1965) reported a greater oxygen debt in smokers during exercise than nonsmokers, but there are no measurements of carboxyhemoglobin to explain the difference. The changes in heart function associated with cigarette

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smoking discussed by Roskamm (1964) and Anderson (1971) related to constituents of cigarette smoke other than carbon monoxide.

3. Myocardial effects in animals. The rat has been the laboratory animal most extensively used to investigate myocardial effects of carbon monoxide. Asmussen and Paulsen (1953) exposed immature rats for 60 days to an atmosphere containing carbon monoxide. The blood levels were kept at 50 to 60% carboxyhemoglobin. Compared with control rats, the carbon-monoxide-treated rats were inferior in their ability to swim till exhausted and to withstand low oxygen tension. The carbon-monoxide-treated rats showed cardiac hypertrophy and a slight but significant increase in the relative number of coronary capillaries. Suzuki (1969) administered 1% carbon monoxide for 10 min to mature rats and the animals were sacrficed from 10 min to 24 hours after cessation of inhalation. The electron microscope examination of the heart revealed intracellular edema, swelling of mitochondria and sacroplasmic reticular, disruption and reduction of cristae, disappearance of mitochondria, appearance of lipofuscin pigment granules and lysosomes and increase of glycogen granules and fat droplets. The author concluded that the effects of carbon monoxide on the heart result not only from hypoxemia but also from the direct toxic effects on the specific respiratory enzymes. Holczabek (1971) arrived at a similar conclusion following exposure of rats to 3% carbon monoxide. Slater (1950) demonostrated inhibition of dihydrocozymase oxidase of heart muscle exposed to carbon monoxide in vitro.

The direct effects of carbon monoxide on the monkey heart have not been investigated. Since there is a species difference relating to pulmonary

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effects, it is reasonable to suspect that this may also apply to the heart. The rabbit heart shows cardiac necrosis, which could be interpreted to be the result of hypoxemia rather than the direct effect of carbon monoxide (Veith, 1940).

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XI-D. Experimental Atherosclerosis

Cigarette smoking causes vasoconstriction of most vascular beds. These effects are brought about by nicotine contained in the smoke. The carbon monoxide absorbed during smoking does not contribute to vascular effects. In animals, the pattern of action of carbon monoxide is vasodilatation with elevation of body temperature (Binet and Burstein, 1948; Coret and Hughes, 1964; Nielsen, 1971). In man vasoconstriction of the hand reflexly induced by cold is reduced by levels of 19 and 25% carboxyhemoglobin (Heistad and Wheeler, 1972).

The influence of carbon monoxide on capillary permeability has been investigated in humans and animals. In man, exposure to carbon monoxide for 8 days caused an increase in the permeability of the capillaries to albumin (Siggaard-Andersen et al., 1969). The increase in permeability could not be demonstrated in the calf muscle (Petersen et al., 1968). In rabbits, guinea pigs and rats there is an increase in permeability in the peritoneal cavity (Göthert et al., 1970) and subcutaneous tissue (Van Liew, 1968 a and b, 1970).

Although no specific case of arterial disease caused by carbon monoxide associated with cigarette smoking has been reported, there have been repeated suggestions of cause and effect relationship. The facts are as follows:

1. In patients with thromboangiitis obliterans or Buerger's disease, Astrup (1964) pointed out a connection between smoking and increased affinity of hemoglobin. Astrup (1966 a and b) and Astrup et al. (1966) showed the increase in affinity for oxygen to be associated with carbon monoxide present

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in tobacco smoke, since higher carboxyhemoglobin levels were observed in smokers with thromboangiitis obliterans than in healthy smokers. Mulhausen et al. (1967) confirmed this observation in another group of patients. Kjeldsen and Mozes (1969) and Kjeldsen (1969) noted in a third group of patients that the carboxyhemoglobin saturations and cholesterol levels are higher in controls. Birnstingl et al. (1966) demonstrated that patients with thromboangiitis obliterans did not show a greater alteration in oxygen affinity produced by smoking than did compared with normal smokers. The possibility that carboxyhemoglobin increases blood viscosity and therefore reduces the velocity of blood circulation and hastens the tendency to thrombus formation, has been excluded by measurements performed by Solvsteen and Kristjansen (1968).

2. That exposure to carbon monoxide could lead to atherosclerosis was proposed by Hueper (1944) as part of his anoxemia theory. Astrup and his collaborators have attempted to find experimental support for this theory in cholesterol-fed rabbits - see reviews by Astrup (1967, 1969, 1970, 1972) and by Astrup and Kjeldsen (1970). The exposure to carbon monoxide enhanced the development of atheromatosis (Astrup et al., 1968, 1970 a and b). The development of the lesions was enhanced by hypoxia and reversed by hyperoxia (Kjeldsen et al., 1968, 1969). The appearance of lesions was accompanied by elevation of serum lipid levels (Truhaut et al., 1968; Astrup et al., 1970 Kjeldsen, 1970a), change in lactate dehydrogenase isoenzymes of the aortic arch (Hellung-Larsen et al., 1968), increased endothelia permeability (Wanstrup et al., 1969), and ultrastructural intimal changes (Kjeldsen et al., 1972). In human subjects exposed to carbon monoxide, an increase in capillary filtration rate (Siggaard-Andersen et al., 1967) and elevation of serum lipid levels (Kjeldsen, 1970b)

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have been demonstrated. It has been suggested that carbon monoxide inhibits synthesis of cholesterol, leading to accumulation of lanosterol (Gibbons and Mitropoulus, 1972). Another effect of carbon monoxide is an increase in mitochondrial enzymic activity, which stimulates lipid synthesis within the artery (Whereat, 1970). Webster et al. (1968) aggravated atherosclerosis by carbon monoxide exposure in monkeys fed with cholesterol containing diet. It has not been possible to develop atherosclerosis in animals exposed to carbon monoxide without supplemental cholesterol feeding.

3. Examination of individuals who have been exposed to an environment of up to 1,000 ppm carbon monoxide with carboxyhemoglobin levels of blood between 2 and 26 % for an average duration of 10.5 years did not reveal any early development of arteriosclerosis (Prerovska and Drdkova, 1967 a and b; 1971). The average values of serum lipid levels did not exceed the normal range. The results of experiments on rabbits do not apply to epidemiologic surveys in humans.

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XI-E. Blood Cells and Plasma

The most consistent effect of the carbon monoxide component of cigarette smoking is the appearance of carboxyhemoglobin in the blood. The molecular basis for the formation of carboxyhemoglobin has been reviewed by Rossi-Fanelli and Antonini (1958), Wittenberg (1966) Keyes et al. (1967), Oski et al. (1970), Bunn and Jandl (1970) and Brewer et al. (1970, 1971) There is a change in oxygen-dissociation curve of blood of smokers (Gutenkauf et al., 1967) and patients with acute myocardial infarction (Eliot and Mizukami, 1967). There is an increase in oxygen affinity of the hemoglobin presumably unrelated to carboxyhemoglobin. The consequences of the presence of carboxyhemoglobin to the circulatory system have been reviewed by Lilienthal (1950), Bartlett (1968), Goldsmith and Landow (1968), Grut et al. (1970) and DuBois (1970).

Exposure to carbon monoxide causes an increase in platelet adhesiveness in atherosclerotic patients (El-Ebrashy et al., 1967) and in rabbits (Birnstingl et al., 1971). There is also an increase in fibrinolytic activity in patients suffering from carbon monoxide poisoning (El-Attar, 1968 a and b) and in experimental animals (Candura and Craveri, 1964).

Four groups of situations are characterized by hematologic changes. They are as follows:

1. Exposure to carbon monoxide in man causes an increase in the red cell and reticulocyte counts and the serum globulin fraction (Coscia et al.,

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1964; Tkachenko et al., 1966; Glass et al., 1968; Kjeldsen and Damgaard, 1968; Bethlenfalvay, 1971a). The erythrocytes manifest some differences from normal erythrocytes in staining (Blackmore, 1970; Bethlenfalvay, 1971b), denaturation of hemoglobin (Perrelli et al., 1970) and a change in the shift of the oxyhemoglobin dissociation curve to the left (Brody and Coburn, 1969).

2. In dogs, exposure to carbon monoxide increases hemoglobin concentration (Asmussen and Vinther-Paulsen, 1949). This change is regarded as an important mechanism for tolerance of acclimatization to carbon monoxide (Otis, 1970). A similar increase in hemoglobin and the red cell count has been noted in other species, such as rabbits (Truhaut et al., 1968), rats (Ramsey, 1969), rhesus monkeys (Theodore et al., 1971), and squirrel monkeys (Jones et al., 1971).

3. Cigarette smoking caused an increase in the red cell count and hemoglobin, whereas abstinence caused a fall in the content of these in humans (Eisen and Hammond, 1956; Pincherle and Shanks, 1967) and in hamsters (Reckzeh and Dontenwill, 1970). In another investigation involving smokers, the elevated hemoglobin and red cell count were correlated with carboxyhemoglobin levels (Petrovic, 1970). A shift in the oxygen dissociation curve to the left has been noted in cigarette smokers (Gutenkauf et al., 1967; Birnstingle et al., 1967).

4. Patients suffering from myocardial ischemia with normal coronary arteriograms have been shown to have abnormal hemoglobin-oxygen dissociation

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(Likoff et al., 1967; Eliot and Bratt, 1969; Guy et al., 1971). There is no evidence that these patients sustain carboxyhemoglobinemia, nor is the ischemia associated with cigarette smoking.

The above examples are clearly different entities. Cigarette smoking is included only in situation 3 and carbon monoxide 1 to 3.

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PART SIX

PUBLICATIONS AND RECOMMENDATIONS

XII. Secondary Publications on Smoking and Heart Disease

XIII. Publications in Defense of Smoking

XIV. Commentary on US Public Health Publications

XV. Recommendations to the Council for Tobacco Research

The last group of sections is largely a commentary on the US Public Health Publications on "Smoking and Health." Following the appearance of the first Surgeon General's Report in 1964, several secondary publications have appeared accepting the statement that smoking is causally related to coronary heart disease. There are only a few publications which challenge this statement. A list of recommendations to the Council for Tobacco Research concludes this report.

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XII. SECONDARY PUBLICATIONS ON SMOKING AND HEART DISEASE

The publications listed in this section are secondary to those which describe the original investigations covered in preceding sections. Since 1864, there has been an increase in the number of publications accepting the Surgeon General's statement that smoking is causally related to coronary heart disease. The number of review articles, editorials, letters and special articles has increased so rapidly that the total number appearing since 1970 approaches the number of articles appearing up to 1964. The total number at various periods is as follows:

	1879-1949	1950-1964	1965-1969	1970-1973
A. Review articles (p. 323)	22	22	14	6
B. Special articles (p. 328)	1	14	29	17
C. Letters to the Editor (p. 332)	1	17	14	26
D. Editorials (signed) (p. 336)	—	14	14	6
E. Editorials (unsigned) (p. 339)	—	14	18	15
F. Miscellaneous articles (p. 342)	—	—	23	7
Total number of articles	24	81	112	77

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XII. SECONDARY PUBLICATIONS ON SMOKING AND HEART DISEASE

A. Review Articles

Reprint

1879

DECAISNE D E: Les femmes qui fument. Rev d'Hygiene Police Sanitaire 1: 914-922, 1879. S 1

1883

VALLIN E: Sur quelques accidents causés par le tabac. Rev Hyg 5: 223-237, 1883. S 2

1885

POTAIN: De l'empoisonnement par le tabac. Sem Med 5: 159-160, 1885. S 3

1887

FAVARGER H: Chronische Tabakvergiftung und ihren Einfluss auf das Herz und den Magen. Wien Med Wochenschr 37: 324-326, 1887. S 4

1892

CHAPMAN W C: Tobacco as a cause of hypertrophy and dilatation of the heart: "The tobacco-heart" with a report of cases. Med News 61: 733-735, 1892. S 5

1902

COUGHLIN R E: The use and abuse of tobacco. N Engl Med Month 323-326, 1902. S 6

1905

BRUNTON L: The effect of tobacco in health and disease. Practitioner 75: 54-57, 1905. S 7

1906

BRUNTON L: The effect of tobacco in health and disease. Med Exam Pract 16: 148-150, 1906. S 8

KAKOWSKI: Ueber den direkten Einfluss verschiedner Substanzen auf das Herz. Arch Int Pharmacodyn Ther 15: 21-139, 1906. S 9

1917

SIEBELT: Tabakmissbrauch in ursächlichem Zusammenhange mit Kriegsneurosen, vor allem des Herzens. Med Klin 13: 68-69, 1917. S 10

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XII A: Review Articles

Reprint

1921

BRIGHAM R O: Heart failure and tobacco as an etiological factor. Ohio State Med J 17: 226-228, 1921. S 11

1923

FÜRBRINGER: Über die Schädigungen durch Tabakrauchen. Z Aerztl Fortbild 20: 697-703, 1923 S 12

1926

FÜRBRINGER: Zur Würdigung der Gefahren des Tabakrauchens. Dtsch Med Wochenschr 52: 2021-2025, 1926. S 13

1929

JOHNSON W M: Tobacco smoking: A clinical study. JAMA 93: 665-667, 1929. S 14

1930

PLENGE K: Tabakabusus und Koronarsklerose. Dtsch Med Wochenschr 56: 1947-1948, 1930. S 15

1937

MINNHAAR T C: Rol patogenético del humo del tabaco en las afecciones del aparato cardiovascular. Rev Med Roasario 27: 706-732, 1937. S 16

1939

HEAD J R: The effects of smoking. Ill Med J 76: 283-287, 1939. S 17

1943

BRIESEMEISTER R: Vom Rauchen und vom frühzeitigen Tod durch Tabakmissbrauch. Med Welt 17: 759-762, 1943. S 18

KUTSCHERA-AICHBERGEN H: Genussgifte. Wien Klin Wochenschr 56: 46-49, 1943. S 19

1944

MARIS R: The facts about smoking. Hygeria 22: 740-741, 1944. S 20

1946

ROSS P H and IVY A C: Tobacco smoking and coronary artery disease. Q Bull Norwest Univ Med Sch 20: 424-440, 1946. S 21

1949

VON AHN B: Elektrokardiogrammet vid tobaksrökning. Nord Med 41: 451-455, 1949. S 21a

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Source: https://www.industrydocuments.ucsf.edu/docs/rrlk0000

XII A: Review Articles Reprint

1950

MILLS C A: Tobacco smoking:Some hints of its biologic hazards. Ohio State Med J 46: 1165-1170, 1950. S 22

1952

SCOTT R B: Some medical aspects of tobacco-smoking. Br Med J 1: 671-675, 1952. S 23

1954

VAN REENEN J F: Tobacco: The effects of its use with special reference to the mouth and dental elements. A survey of the literature. J D A S A 9: 334-347, 1954. S 24

1955

HEGGLIN R and KEISER G: Über Rauchen und Coronarerkrankungen. Schweiz Med Wochenschr 85: 53-55, 1955. S 25

SIGLER L H: Tobacco as a contributing cause of degenerative coronary disease. N Y State J Med 55: 3107-3113, 1955. S 26

1956

COFFIN G J: The effects of tobacco smoking. Bull N Y Acad Med 32: 133-156, 1956. S 27

JOULES H: Tobacco and smoking. Postgrad Med J 32: 226-231, 1956. S 28

1958

ROTH G M and SHICK R M: Effect of smoking on the cardiovascular system of man. Circulation 17: 443-459, 1958. S 29

1959

KUMLIN T: Tupakan vaikutuksesta verenkiertoon sekä kokemuksia tupakanieroitushoidosta. Duodecin 75: 1-9, 1959. S 30

1960

BRONTE-STEWART B: The relationship of smoking to ischemic heart disease. S Afr Med J 34: 511-512, 1960. S 31

MONASTERIO G: Un grave pericolo per la salute: il tabagismo. Riforna Med 74: 989-996, 1960. S 32

ROTH G M: Recent developments in the effects of smoking and nicotine on the cardiovascular system of man. Mod Concepts Cardiovasc Dis 29: 605-610, 1960. S 33

1961

BRONTE-STEWART B: Cigarette smoking and ischemic heart disease. Clin Med 8: 1359, 1361-1362, 1364, 1961. S 34

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XII A: Review Articles

Reprin

LUPU N G, POPESCU I and ENESCU V: Actiunea fumatului asupra aparatului cardio-vascular. Med Intern 13: 347-351, 1961. S 35

SACHDEV J R and WAHI P L: Tobacco and heart disease. Indian Pract 14: 717-723, 1961. S 36

1962

DELARUE N C: Cigarette smoking: A clinical and public health challenge. Can Med Assoc J 87: 961-969, 1962. S 37

HAMMOND E C: The effects of smoking. Sci Am 207: 39-51, 1962. S 38

1963

PAUL O: Cigarette smoking and cardiovascular disease. Public Health News 44: 223-224, 1963. S 39

1964

DOYLE J T: Tobacco and the circulation apparatus. Natl Conf Cardiovasc Dis 2: 361-362, 1964. S 40

GIOVANELLI E: Gli effetti del fumo di tabacco sul cuore e sue possibili influenze nell'insorgenza e nel decorso delle affezioni cardiache. Minerva Med 55: 1529-1542, 1964. S 41

PAUN D: Tabak und Koronarinsuffizenz. Z Aerztl Fortbild 58: 690-693, 1964. S 42

SCHIRGER A and SHICK R M: Tobacco in cardiovascular disease. Minn Med 47: 129-132, 1964. S 43

1965

CRAMER K: Rökning och coronarsjukdom. Lakartidningen 62: 2532-2540, 1965. S 44

RAAB W: Origin, prediction and prevention of ischemic heart disease. J Circ J 29: 113-122, 1965. S 45

1967

ANSELMINO A and BOSCO M: Tabacco e cuore. Minerva Med 58: 1298-1308, 1967. S 46

KREYBERG L, DABLE T, POPPE E, EFSKIND L, PEDERSEN E, ELDJARN L, and DEVIK F: Tobakkroking og helse. Tidsskr Nor Laegeforen 87: 1007-1013, 1967. S 47

1968

ANONYMOUS: Il fumo di tabacco nei suoi aspetti dottrinali, clinici e sociali. Minerva Med 59: 2262-2264, 1968. S 48

DOYLE J T: Tobacco and heart disease. Postgrad Med 44: 188-191, 1968. S 49

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Source: https://www.industrydocuments.ucsf.edu/docs/rrlk0000

XII A: Review Articles

Reprint

DOYLE J T: Importance of dose response in terms of total cigarette smoke, "tar", and nicotine: Cardiovascular system. Natl Cancer Inst Monogr 28: 43-46, 1968. S 50

JAMES G: Summary: Highlights on smoking and the heart. Bull N Y Acad Med 44: 1559-1565, 1968. S 51

KOLLER S: Lebensverkurzung durch Lungenkrebs und Kreislaufschaden als Folge des Zigarettenrauchens. DA 4: 191-206, 1968. S 52

OETTEL H: Toxische Gefässchaden und Durchblutungsstörungen. Kippokrates 8: 285-295, 1969. S 53

SANTRŮČEK M and VACEK M: Kouření a ischemická choroba srdeční ve světle epidemiologických studií. (Smoking from the aspect of epidemiological investigation). Cas Zdrav 16: 66-75, 1968. S 54

1969

DOYLE J T: Smoking and myocardial infarction. Circulation 39-40 (Suppl 5): 136-143, 1969. S 55

FITZGERALD P: Arterial disease and tobacco. Anesth Analg 48: 412-417, 1969. S 56

SCHWEIZER W: Die medizinische Behandlung der koronaren Herzkrankheit. Dtsch Med Wochenschr 94: 2646-2649, 1969. S 57

1970

FLETCHER C M and HORN D: Smoking and health. WHO Chron 24: 345-370, 1970. S 58

GODBER G E: Smoking disease: A self-inflicted injury. Am J Public Health 60: 235-242, 1970. S 59

1971

JAN F and GROSGOGEAT Y: Tabac et coronaires. Vie Med 52: 3019-3026, 1971. S 60

SWARTZ H: Tobacco smoke: A noxious air pollutant. Rev Allerg 25: 397-405, 1971. S 61

1972

HAY D R: Smoking and health: The 1972 situation. N Z Med J 76: 4-12, 1972. S 62

SCHIEVELBEIN H and EBERHARDT R: Cardiovascular actions of nicotine and smoking. J Natl Cancer Inst Monogr 48: 1785-1794, 1972. S 63

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XII. SECONDARY PUBLICATIONS ON SMOKING AND HEART DISEASE

B. Special Articles

Reprint

1939

HARRIS S: Medical and public health needs and advice to young doctors. J Med Assoc Ala 8: 369-386, 1939. S 64

1951

MORRIS J N: Recent history of coronary disease. Lancet 1: 1-7, 1951. S 65

1958

REID D D: The epidemiology of coronary disease. Practitioner 180: 184-190, 1958. S 66

1960

BLACKBURN H, BROZEK J, TAYLOR H L and KEYS A: Comparison of cardiovascular and related characteristics in habitual smokers and nonsmokers. Ann N Y Acad Sci 90: 277-289, 1960. S 67

1962

PRESCOTT F: The smoking problem in Britain. Appl Ther 4: 1018-1023, 1962. S 68

1963

WHITE P D: Heart disease -- a matter of concern to executives. Arch Environ Health 6: 309-311, 1963. S 69

1964

ALIMURUNG M M: Conspirators of the heart. Santo Tomas J Med 19: 290-292, 1964. S 70

BLAKE J M: Self-induced air pollution: smoking. N Y State J Med 64: 806-810, 1964. S 71

British Medical Journal: Deaths from smoking. 1: 451-452, 1964. S 72

FLICK J B Jr: The cigarette smoking problem. Delaware Med J 36: 51-53, 1964. S 73

KANNEL W B: Cigarette smoking and coronary heart disease. Ann Intern Med 60: 1103-1106, 1964. S 74

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XII B: Special Articles

Reprint

LEAMAN W G: Tobacco and heart disease: Is further research necessary? Pa Med J 67: 22, 1964. S 75

OCAMPO OTERO A: Efectos perjudiciales del tabaco. Med Segruided Trabajo Madrid 12: 78-82, 1964. S 76

PLATT R: Public persuasion in health matters with particular reference to smoking. Proc R Soc Med 57: 449-458, 1964. S 77

WILENS S L: Relation of tobacco smoking to cardiovascular disease. Natl Conf Cardiovasc Dis 2: 360-361, 1964. S 78

1965

FARBER R E: Cancer deaths rise in 1964. Md State Med J 14: 81-82, 1965. S 79

KISTLER H J: Coronare Herzkrankheit und Zigarettenrauchen. Schweiz Med Wochenschr 95: 436-437, 1965. S 80

NAHUM L H: Smoking and thrombosis. Conn Med 29: 853-854, 1965. S 81

RAVENHOLT R T: Cigarette smoking: Magnitude of the hazard. CA 15: 187-188, 1965. S 82

SCHMIDT F: Zigarette und Lungenkrebs. Med Welt 35: 1948-1956, 1965. S 83

WILLIAM-OLSSON L: Rökning och blodsocker. Läkartidningen 62: 3810-3811, 1965. S 84

1966

BLOMSTRAND R and LUNDMAN T: Serum lipids and heredity. Acta Med Scand Suppl 455: 51-60, 1966. S 85

HINKLE L E, BENJAMIN B, CHRISTENSON W N and ULLMANN D S: Coronary heart disease. Arch Environ Health 13: 312-321, 1966. S 86

MULCAHY R: Public health aspects of cigarette smoking, with a note on public and professional attitudes. J Ir Med Assoc 58: 82-88, 1966. S 87

1967

BIENER K: Rauchen und Coronarsklerose. Schweiz Med Wochenschr 97: 59-60, 1967. S 88

CHAPMAN J S: Smoking and health. Am Rev Resp Dis 96: 613-622, 1967. S 89

SIRTORI C: Analisi scientifica e sociale del fumo. Minerva Med 58: 299-300, 1967. S 90

STUBER R V: Smoking -- where do we stand? Mich Med 66: 324, 329, 1967. S 91

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Source: https://www.industrydocuments.ucsf.edu/docs/rrlk0000

XII B: Special Articles

Reprint

1968

CHIEF MEDICAL OFFICER OF THE MINISTRY OF HEALTH: Smoking and health. In: On the State of the Public Health, Her Majesty's Stationery Office, Vol 1, pp. 241-245, 1968. S 92

FISHER G R: Associated clinical societies. Delaware Med J 40: 364-365, 1968. S 93

FREDRICKSON D T: How I help people stop smoking. Hosp Physician 4: 52-56, 1968. S 94

FODOR J T, GLASS L H and WEINER J M: Smoking behavior, cognitive skills and educational implications. J School Health 38: 94-98, 1968. S 95

GREEN D E and HORN D: Physicians' attitudes toward their involvement in smoking problems of patients. Dis Chest 54: 12-13, 1968. S 96

HARKEN D E: Smoking....The masochistic massacre. Dis Chest 54: 47-51, 1968. S 97

OCHSNER A: Prevention of executive obsolescence. J Am Geriatr Soc 16: 1077-1082, 1968. S 98

PAUL O: Smoking and youth. Ind Med Surg 287-288, 1968. S 99

ORAM S: Smoking and ischaemic heart disease. Br Heart J 30: 145-150, 1968. S 100

PAUL O: Stimulants and coronaries. Postgrad Med 44: 196-199, 1968. S 101

SCHUMANN L M: Epidemiology of smoking related diseases which physicians encounter in their office practice. Dis Chest 54: 8-11, 1968. S 102

TERRIS M: A social policy for health. Am J Public Health 58: 5-12, 1968. S 103

1969

DLIN B M: The doctor, his emotions and his heart. Minn Med 52: 369-374, 1969. S 104

DOYLE J T: Cigarette smoking. The associated cardiovascular risk. Minn Med 52: 1311-1313, 1969. S 105

FOX W: A homeopath looks at coronary disease. J Am Inst Homeopath 62: 6-9, 1969. S 106

SACKETT D L: Cigarettes, alcohol, hospitals, and atherogenesis. Am Heart J 78: 423-424, 1969. S 107

1970

DIEHL H S: The physician and cigarette smoking. New Physician 19: 231-234, 1970. S 108

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Source: https://www.industrydocuments.ucsf.edu/docs/rrlk0000

XII B: Special Articles — Reprint

FREDRICKSON D T: Cigarette smoking: Questions patients ask doctors. Chest 58: 147-151, 1970. S 109

LISZEWSKA D and MICHALSKI E: Czynnik ryzyka choroby wieńcowej. Pol Tyg Lek 25: 1140-1142, 1970. S 110

MUSHIN W W: The normality of the abnormal. Anesth Analg 49: 667-679, 1970. S 111

TIBBLIN G and WILHELMSEN L: 1913 års män -- rökare och icke-rökare. Läkartidningen 67: 278-281, 1970. S 112

1971

BOSE A K: Economics and dangers of smoking. J Indian Med Assoc 56: 320, 1971. S 113

FLETCHER C M: Environmental hazards. The hazards of smoking. Mod Med Gt Britain 16: 723-726, 1971. S 114

HEDRICK J L: The economic costs of cigarette smoking. HSMHA Health Rep 86: 179-182, 1971. S 115

HIPSLEY E H: Med J Australia 1: 1146, 1971. S 116

KEMP R: Patients and cigarettes. Practitioner 207: 215-220, 1971. S 117

MEIJLER F L: Arts en roken. Ned Tijdschr Geneeskd 115: 511-513, 1971. S 118

PUNSAR S: Tupakointi ja sepeivaltimotauti. Suom Laakarilehti 26: 27-32, 1971. S 119

TERRY L L: The future of an illusion. Am J Public Health 233-240, 1970. S 120

UDRY J R: A spoonful of sugar helps the medicine go down. Am J Public Health 61: 776-785, 1971. S 121

1972

BALL K H: Cigarettes and the prevention of heart disease. Rehabilitation 25: 17-20, 1972. S 122

SELTZER C C: Critical appraisal of the Royal College of Physicians' report on smoking and health. Lancet 1: 243-248, 1972. S 123

WYNDER E L and HOFFMANN D: Less harmful ways of smoking. J Natl Cancer Inst 48: 1749-1758, 1972. S 124

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XII. SECONDARY PUBLICATIONS ON SMOKING AND HEART DISEASE

C. Letters to the Editor

Reprint

1934

BLUMER G: The relation of the use of alcohol and tobacco to coronary occlusion. JAMA 102: 1177, 1934. S 125

1951

PARNELL R W: Smoking and cancer. Lancet 1: 963, 1951. S 126

1953

LEVY R L, KNIGHT G F, MYERSON M C and ROSEN F L: Effects of tobacco smoking. Mod Med 21: 120-121, 1953. S 127

1955

OLBERT T: Smoking and the heart. Lancet 2: 1041, 1955. S 128

1958

FISHER R A: Lung cancer and cigarettes? Nature 182: 108, 1958. S 129

1960

ACHESON R M: Atherosclerosis and coronary heart disease. Lancet 2: 706, 1960. S 130

CHARTERS A D and ARYA B P: Incidence of ischaemic heart disease among Indians in Kenya. Lancet 1: 288-289, 1960. S 131

RIGDON R H: The smoking controversy. JAMA 173: 293-295, 1960. S 132

1962

GARLAND L H: Smoking and health. N Engl J Med 267: 627-628, 1962. S 133

HECHT S D: Cause and effect. N Engl J Med 267: 312, 1962. S 134

HUGHES J P W: Civilisation and peptic ulcer. Lancet 1: 322, 1962. S 135

LUKE E: Addiction to mentholated cigarettes. Lancet 1: 110-111, 1962. S 136

RIGDON R H: To the editor. Ind Med Surg 31: 235, 1962. S 137

1963

OPSTAD E T: Smoking and heart disease. N Engl J Med 268: 903, 1963. S 138

SHEKELLE R B and OSTFELD A M: Stress and occlusive coronary artery disease. Lancet 2: 1393-1393, 1963. S 139

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XII C: Letters to the Editor

Reprint

1964

ANONYMOUS: Smoking and the heart. Br Med J 2: 296, 1964. S 140

RAVENHOLT R T: Cigarette smoking: Magnitude of the hazard. Am J Public Health 54: 1923-1926, 1964. S 141

WAKELEY C: Deaths from smoking. Br Med J 1: 1634, 1964. S 142

1965

DORMANDY T L: Abnormal oxygen-dissociation curves. Lancet 2: 80-81, 1965. S 143

RICHARDSON R D, WALKER A R P and WALKER B F: Glycosuria and coronary heart-disease. Lancet 2: 594-595, 1965. S 144

ROTHERMICH N O: Work after a "coronary". Br Med J 1: 860, 1965. S 145

WILLIAM-OLSSON L: Smoking and platelet stickiness. Lancet 2: 908-909, 1965. S 146

1966

BURCH P R J and ROWELL N R: Smoking and atherosclerosis. Br Med J 1: 1050-1051, 1966. S 147

SZANTO S: Smoking and atherosclerosis. Br Med J 1: 984, 1966. S 148

1967

SALTER A J: The anti-coronary club. Lancet 1: 336, 1967. S 149

SZANTO S: Smoking and atherosclerosis. Br Med J 3: 178, 1967. S 150

1968

ASHER R: Trial of unsaturated-fat diet. Lancet 2: 1191, 1968. S 151

GRANT B J B: The nicotine habit. Lancet 1: 645, 1968. S 152

LACY B S: Smoking and the coronary arteries. Am Med Assoc 204: 1009, 1968. S 153

MAGNUSON W G: Smoke screen. 55: 1102, 1968. S 154

1969

DENHAM R M: Smoking and the coronary circulation. GP 39: 129, 1969. S 155

WALKER A R P: Sugar intake and coronary heart disease. Lancet 2: 1071, 1969. S 156

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Source: https://www.industrydocuments.ucsf.edu/docs/rrlk0000

XII C: Letters to the Editor

Reprint

1970

BALL K: Hospital beds and cigarette smoking. Lancet 2: 48, 1970. S 157

DAYTON S and PEARCE M L: Diet and atherosclerosis. Lancet 1: 473-474, 1970. S 158

PAFFENBARGER R S: Occupational preselections. N Engl J Med 283: 100, 1970. S 159

YUDKIN J: Sugar, cigarettes, and heart-disease. Lancet 1: 1111, 1970. S 160

1971

BLACKET R: Coronary heart disease and diet. Med J Australia 1143-1144, 1971. S 161

CLEAVE T L: Sugar intake and myocardial infarction. Lancet 1: 43, 1971. S 162

DALDERUP L M: Mutants, hyperlipoproteinaemia, and coronary artery disease. Br Med J 2: 771, 1971. S 163

GILDER: Smoking and the physician. Can Med Assoc J 104: 476, 1971. S 164

GRANNIS G F: Cigarettes and heart disease. N Engl J Med 284: 1384-1385, 1971. S 165

HIPSLEY E H: Diet and heart disease. Med J Australia 2: 219-220, 1971. S 166

MORGAN L: Diet and heart disease. Med J Australia 2: 282-283, 1971. S 167

SELTZER C C: Cigarettes and heart disease. N Engl J Med 284: 557-558, 1971. S 168

TURNER R W D and ILLINGWORTH D G: Prevention of coronary deaths. Br Med J 4: 228, 1971. S 169

1972

BALL K P: Preventable smoking deaths. Lancet 1: 201, 1972. S 170

CHERRY W H and FORBES W F: Smoking and health. Lancet 2: 824-825, 1972. S 171

FLETCHER C M: Smoking and health. Lancet 1: 386, 1972. S 172

FRIBERG L: Smoking and health. Lancet 2: 973, 1972. S 173

FURST A L, GREAVES D A, HAWTHORNE V M, McCARTNEY H and STEWART G T: Candidates for coronaries. Br Med J 4: 366-367, 1972. S 174

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Source: https://www.industrydocuments.ucsf.edu/docs/rrlk0000

XII C: Letters to the Editor

Reprint

HOWELL R W: Smoking and vascular disease. Br Med J 2: 232, 1972. S 175

HOWELL R W: Serum-cholesterol and smoking. Lancet 1: 901, 1972. S 176

REDGRAVE T G: Oh, Mr Snedden. Med J Australia 1: 196-197, 1972. S 177

SPITTLE C: Atherosclerosis and Vitamin C. Lancet 1: 798, 1972. S 178

WAKEHAM H R R: Smoking and health. Lancet 2: 275-276, 1972. S 179

1973

DALDERUP L M: Coffee drinking and acute myocardial infarction. Lancet 1: 104, 1973. S 180

ELKELES A: Coronary artery disease. Br Med J 1: 51, 1973. S 181

SELTZER C C: Smoking and coronary heart disease. N Engl J Med 288: 1186, 1973. S 182

YUDKIN J: Coffee drinking and acute myocardial infarction. Lancet 1: 211, 1973. S 183

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XII. SECONDARY PUBLICATIONS ON SMOKING AND HEART DISEASE

D. Editorials (Signed)

Reprint

1957

WHITE P D: The patient leads the way. Dis Chest 32: 368-376, 1957. S 184

1958

FORBES J: Danger! Doctors at work. Lancet 2: 1226-1227, 1958. S 185

1962

NAHUM L H: Smoking and physiological age. Conn Med 26: 593-594, 1962. S 186

PEABODY J W Sr: Role of cigarette smoking in the causation of disease. Med Ann 31: 702-703, 1962. S 187

KOSHY M C: Diet and vascular disease. 437-439, 1962. S 188

RENTCHNICK P: Is tobacco harmful? Appl Ther 4: 926-927, 1962. S 189

1963

ALVAREZ W C: Smoking and heart disease. Geriatrics 18: 879, 1963. S 190

DOCK W: The ballistocardiographic smoking test. JAMA 186: 509-510, 1963. S 191

MacDONALD I: Physicians -- not physicists. Bull Los Angeles Coll Med Assoc 5, 1963. S 192

OVERHOLT R: Observations on smoking. N Engl J Med 268, 54, 1963. S 193

1964

CARRUTHERS W: Hazards of smoking. Nature 203: 221-222, 1964. S 194

FLASER L F: More on smoking and health. Chemistry 18-19, 1964. S 195

COOKE A: Cigarettes -- The final indictment. CA 14: 35-36, 1964. S 196

HISLOP H J: That cloud of smoke. J Am Phy Ther Assoc 44: 155, 1964. S 197

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Source: https://www.industrydocuments.ucsf.edu/docs/rrlk0000

XII D: Editorials (Signed) — Reprint

1967

HAMMOND E C: Intelligent debate or demented fiddling? Can Med Assoc J 96: 679-680, 1967. S 198

PAGE I H and ALVAREZ W C: Cigarettes and the ambivalent American. Mod Med 35: 59-61, 1967. S 199

VELA J E: Tabaquismo y corazon. Arch Inst Cardiol Mex 37: 539-540, 1967. S 200

1968

ABELSON P H: Changing attitude toward smoking. Science 161: 319, 1968. S 201

PAVITT L: Cigarettes (Health hazards). R Soc Health J 88: 223, 1968. S 202

REID D D: Smoking and the heart. Health 5: 176-177, 1968. S 203

SCHATTENBERG T T: Exercise -- The heart and the doctor athlete. Minn Med 51: 1577, 1968. S 204

1969

ADAMS S I: The stresses of urban living. Health 19: 12-15, 1969. S 205

ADAMS C W: Prevention by aggression. Dis Chest 55: 95-96, 1969. S 206

ANONYMOUS: Serum-uric-acid and coronary heart-disease. Lancet 1: 358, 1969. S 207

CARTER L J: Smoking and health: Closing the ring on the cigarette. Science 164: 1258-1261, 1969. S 208

DIEHL H S: Opportunity unlimited. Minn Med 52: 699-701, 1969. S 209

MUELLER M: Anti-smoking forces gain ground. Science 165: 569, 1969. S 210

OETTEL H: Krebsgefährdung durch Rauchbestandteile? Med Klin 64: 463-464, 1969. S 211

1970

GREENBERG S R and WHEREAT A F: Atherosclerosis and mitochondria. Ann Intern Med 73: 861-862, 1970. S 212

1971

ADAMS F H: Prevention of coronary disease -- Let's begin with the children! Am J Cardiol 28: 745, 1971. S 213

LISTER J: Smoking and health now. N Engl J Med 284: 656-657, 1971. S 214

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XII D: Editorials (Signed) — Reprint

LITTLE D M Jr: Physician, heal thyself. Anesthesiology 35: 1-3, 1971. — S 215

PAGE I H: A personal view on diet and atherosclerosis. Mod Med 39: 49-52, 1971. — S 216

1972

BENNETT J S: Smoking: Time to practice what we preach. Can Med Assoc J 106: 276, 278, 1972. — S 217

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XII. SECONDARY PUBLICATIONS ON SMOKING AND HEART DISEASE

E. Editorials (Unsigned)

1955

British Medical Journal: Smoking and coronary thrombosis. 1: 91-92, 1955. S 21

1956

British Medical Journal: Smoking and the cardiovascular system. 2: 90, 1956. S 21

1963

British Medical Journal: Prevention of myocardial infarction. 2: 1351-1352, 1963. S 22

British Medical Journal: Smoking and blood clotting. 1: 833-834, 1963. S 22

Journal of the American Medical Association: Tobacco, pollution, and pesticides. 155: 31-33, 1963. S 22

1964

American Journal of Public Health: Cigarette smoking and health. 54: 322-324, 1964. S 22

British Medical Journal: Work after a "coronary". 2: 703-704, 1964. S 22

British Medical Journal: Healthier life. 1: 1267-1268, 1964. S 22

British Medical Journal: Smoking and death. 1: 192-194, 1964. S 22

Canadian Medical Association Journal: Smoking once more. 91: 353-354, 1964. S 22

Journal of the American Medical Association: Childish habit. 189: 850, 1964. S 22

Lancet: Haemoglobin changes in Buerger's disease. 2: 1164, 1964. S 22

Lancet: Coronary-artery disease in the young. 2: 628-629, 1964. S 23

Medical Journal of Australia: The United States report on smoking and health. 51: 201-202, 1964. S 23

1965

Medical Journal of Australia: National health. 1: 205-206, 1965. S 23

Public Health Reports: Relate heavy cigarette smoking to angina. 60: 121, 1965. S 23

1966

British Medical Journal: Smoking and atherosclerosis. 1: 755-756, 1966. S 23

British Medical Journal: Cigarette smoking and heart disease. 2: 1404-1405, 1966. S 23

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XII E: Editorials (Unsigned) Reprint

Journal of the American Medical Association: The martyred meal. 198: 1362-1363, 1966. S 236

1967

Boletin de la Association Medica de Puerto Rico: Cigarette smoking and health characteristics. 59: 293-295, 1967. S 237

1968

Food and Cosmetics Toxicology: The scourge of the tobacco industry. 6: 797-799, 1968. S 238

Journal of the Medical Association of Georgia: Coronary heart disease and smoking. 58: 440, 1968. S 239

Medical Journal of Australia: Social status and coronary heart disease. 2: 635-636, 1968. S 240

Medical Officer: Royal institute of Public Health and Hygiene conference, Bristol. 120: 187-190, 1968. S 241

Philadelphia Medicine: Cigarette smoking -- A call to arms. 64: 587, 1968. S 242

1969

American Journal of Public Health: Life styles in the prevention of coronary heart disease. 59: 1568-1569, 1969. S 243

British Medical Journal: Menace of smoking. 3: 753-754, 1969. S 244

British Medical Journal: Coronary disease and competitiveness. 1: 1-2, 1969. S 245

Lancet: More effects of cigarettes. 1: 1012-1013, 1969. S 246

Lancet: Blood-groups and serum-cholesterol. 2: 625, 1969. S 247

Medical Journal of Australia: Smoking and health. 1: 84, 1969. S 248

Public Health Report: Smoking and health. 83: 225, 1968. S 249

1970

Circulation: Some problems. 41 (Suppl 1): 184-185, 1970. S 250

Lancet: The longshoreman's life. 2: 87, 1970. S 251

Lancet:

Medical Journal of Australia: Myocardial infarction and cerebrovascular accidents. 2: 1106, 1970. S 253

Medical Journal of Australia: To smoke or not to smoke. 1: 346-347, 1970. S 254

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XII E: Editorials (Unsigned)

Reprint

1971

British Medical Journal: Coronary deaths. 4: 64, 1971. S 255

British Medical Journal: World action on smoking. 4: 64, 1971. S 256

British Medical Journal: The smoking disease. 1: 61-62, 1971. S 257

Journal of the American Medical Association: Exercise and the heart. 215: 974-975, 1971. S 258

Journal of the American Medical Association: Prevention of CHD: The fat's in the fire. 215: 1813, 1971. S 259

Lancet: Counterblasts to tobacco. 1: 69-70, 1971. S 260

New Zealand Medical Journal: The coronary problem. 74: 332-335, 1971. S 261

1972

British Medical Journal: Predicting coronary artery disease. 4: 3, 1972. S 262

British Medical Journal: Smoking and vascular disease. 2: 3-4, 1972. S 263

Canadian Medical Association Journal: Smoking and health. 106: 313, 1972. S 264

1973

American Journal of Clinical Nutrition: Diet and coronary heart disease. 26: 53-54, 1973. S 265

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XII. SECONDARY PUBLICATIONS ON SMOKING AND HEART DISEASE

F. Miscellaneous Articles

Reprint

1963

Journal of the American Medical Association: Cigarette smoking and blood lipids. 184: 201-202, 1963. S 266

Medical Science: Cardiology. Coronary disease in young people. 13: 720, 722, 1963. S 267

1964

Pennsylvania Medical Journal: Predisposing factors in coronary heart disease. 67: 36, 1964. S 268

Pennsylvania Medical Journal: Pulmonary emphysema and the heart. 67: 24, 1964. S 269

1965

Medical College of Virginia Quarterly: Panel on atherosclerosis. 1: 36-39, 1965. S 270

Quarterly Journal of Medicine: 34: 484, 1965. S 271

1966

Journal of the Medical Association of America: Smokers' blood clots more rapidly. 197: 36, 1966. S 272

Journal of the Medical Association of America: Coronary disease prognosis sought from 100,000 persons. 197: 46-47, 1966. S 273

Pennsylvania Medicine: Public health aspects of heart disease. 66: 41, 1966. S 274

1967

El Dia Medico: La costumbre de fumar. 265, 1967. S 275

1968

British Medical Journal: Smoking habits. 1: 64-65, 1968. S 276

Bulletin of the Los Angeles City Medical Association: Smoking and chronic bronchopulmonary disease. 98: 57-58, 1968. S 277

Bulletin of the Los Angeles City Medical Association: The health consequences of smoking. A public health review: 1967. 1-2, 1968. S 278

Disease of the Chest: Formal recommendations of the National Forum on office management of smoking problems. 4-5, 1968. S 279

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XII F: Miscellaneous Articles

Reprint

Hospital Medicine: Axioms on coronary heart disease. 4: 71, 1968. S 280

Missouri Medicine: Miscellany. 65: 711-712, 1968. S 281

1969

British Heart Journal: Dietry sugar intake and ischaemic heart disease. 31: 792-793, 1969. S 281

British Medical Journal: Cigarette advertising. 2: 833, 1969. S 282

El Dia Medico: Las enfermedades de la civilizacion. 856, 1969. S 283

Journal of the American Medical Association: Call for cigarette curbs. 210: 2293, 1969. S 284

Journal of the American Medical Association: Researchers say smoking causes aortic atherosclerosis. 207: 664-666, 1969. S 285

Medicina Sociale: Congressi e riunioni di interesse medico-sociale. 19: 73-74, 1969. S 286

Pediatria de Actualidad: Aterosclerosis en Pediatria. , 1969. S 287

1970

British Medical Journal: Labelling of cigarette packets. 1: 312, 1970. S 288

Canadian Medical Association Journal: No smoking signs at WHO Headquarters. 102: 996, 1970. S 289

Journal of the American Medical Association: The good life and long life just may go together. 214: 1636, 1970. S 290

1971

Schweizerische Medizinische Wochenschrift: Ärzte als Zigarettenraucher 101: 1420-1421, 1971. S 291

1972

Journal of the American Medical Association: Psychiatrists shrink from giving up cigarettes. 219: 823, 826-828, 1972. S 292

Journal of the American Medical Association: Carbon monoxide linked to heart disease. 221: 456-457, 1972. S 293

Modern Medicine: Heart research offers a boost for exercise -- and a warning. 40: 26, 28, 1972. S 294

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XIII. PUBLICATIONS IN DEFENSE OF SMOKING

The 35 articles listed in this section include eight articles which challenge the conclusions that appeared in the Surgeon General's Report. The following articles are quoted in the Commentary Section.

	Copies appearing on page
Examination of statistical methods:	
Brownlee K A: A review of "Smoking and Health". J Am Stat Assoc 60: 722-739, 1965.	353 (a)
Saiger G L: A critique on the report of the Surgeon General's advisory committee on smoking and health. Bull Int Stat Inst 41: 856-860, 1966.	357 (a)
Sterling T D: A review of the claim that excess morbidity and disability can be ascribed to smoking. J Am Stat Assoc 66: 251-257, 1971.	461 (a)
Oster K A: Prevention of atherosclerosis: Fact or fiction? Med Counterpoint 4: 13-27, 1972.	344 (a)
Examination of epidemiologic and experimental data:	
Cohen J and Heimann R K: Heavy smokers with low mortality. Ind Med Surg 31: 115-120, 1962.	352 (a)
Hutchison G B: The nature of epidemiologic evidence: Smoking and health. Bull N Y Acad Med 44: 1471-1475, 1968.	355 (a)
Seltzer C C: An evaluation of the effect of smoking on coronary heart disease. JAMA 203: 193-200, 1968.	382 (a)
Seltzer C C: The effect of cigarette smoking on coronary heart disease. Arch Environ Health 20: 418-423, 1970.	425 (a)

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XIII. PUBLICATIONS IN DEFENSE OF SMOKING

	Reprint
ANONYMOUS: Smoking. JAMA 186: 32-33, 1963.	S 293
ANONYMOUS: Bulletin on tobacco. N Engl J Med 268: 1087, 1963.	S 296
ANONYMOUS: The Canadian Medical Association brief to the National Conference on Smoking and Health, Ottawa. 89: 1154-1156, 1963.	S 297
ANONYMOUS: The Association presents its views about smoking. Coll Health 14: 2-3, 1965.	S 299
ANONYMOUS: Studies broaden data on smoking and health. JAMA 210: 1377-1378, 1967.	S 299
ANONYMOUS: Cigarette consumption down slightly after five years of smoking debate. JAMA 207: 475-476, 1969.	S 300
ANONYMOUS: The air we breathe. JAMA 208: 353, 1969.	S 301
ANONYMOUS: The longshoreman's life. Lancet 2: 87, 1970.	S 302
ANONYMOUS: Should a strong attempt be made to get old people to change habits like smoking and overeating. Geriatrics 25: 68, 71, 1970.	S 303
ANONYMOUS: Does it help to stop smoking? Lancet 1: 238-239, 1972.	S 304
ANONYMOUS: Cigarettes and heart disease. N Engl J Med 284: 1384, 1971.	S 305
ALTSCHULE M D: Dangerous living. Med Sci 13: 337, 1963.	S 306
ARNOLD C B: Smoking and coronary atherosclerosis. N Engl J Med 273: 1284-1285, 1965.	S 307
BELL J A E: Mortality rates of smokers. Chem Eng News 48: 1970.	S 308
BERKSON J: Statistics and tobacco. JAMA 172: 967-969, 1960.	S 309
BOURKE G J: The opinions of some medical students on smoking, career, and fluoridation. J Ir Med Assoc 154-156, 19	S 310
BRASS A: Tobacco and health. Report of Scottsdale Research Conference. JAMA 213: 1879-1880, 1970.	S 311
BROWN R C: Manifestations of atherosclerosis. JAMA 222: 488, 1972.	S 312
BROWNLEE K A: A review of "Smoking and Health". J Am Statist Assoc 60: 722-739, 1965.	S 313
CHEDD G and STUBBS P: Smoking may not cause coronaries. New Scientist 43: 222, 1961.	S 314
COHEN J and HEIMANN R K: Heavy smokers with low mortality. Ind Med Surg 31: 115-120, 1962.	S 315

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FIESSINGER C: Tobacco angina pectoris. JAMA 60: 1473, 1913. S 316

HUTCHISON G B: The nature of epidemiologic evidence: Smoking and health. Bull N Y Acad Med 44: 1471-1475, 1968. S 317

JORES A: Arzt, Tabak und Alkohol. Dtsch Arzt 13: 752, 754-755, 1964. S 318

KASPARIAN H: Ethanol, smoking evaluated with coronary blood flow. JAMA 190: 33, 1964. S 319

MAJEKODUNMI M A: Seventeenth World Health Assembly. WHO Chron 18: 117-127, 1964. S 320

OSTER K A: Predisposition to atherosclerosis. JAMA 222: 704, 1972. S 321

OSTER K A: Prevention of atherosclerosis: Fact or fiction? Med Counterpoint 4: 13-27, 1972. S 322

SAIGER G L: A critique on the report of the Surgeon General's advisory committee on smoking and health. Bull Int Stat Inst 41: 856-860, 1966. S 323

SCHOENBERGER J A: Mass screening identifies high-risk coronary patients. Postgrad Med 48: 37, 1970. S 324

SELTZER C C: An evaluation of the effect of smoking on coronary heart disease. JAMA 203: 193-200, 1968. S 325

SELTZER C C: The effect of cigarette smoking on coronary heart disease. Arch Environ Health 20: 418-423, 1970. S 326

SOMMER R M: Nonspecification of tobacco smokers. JAMA 222: 487, 1972. S 327

STERLING T D: A review of the claim that excess morbidity and disability can be ascribed to smoking. J Am Stat Assoc 66: 251-257, 1971. S 328

WALKER A R P: The prevention of coronary heart disease. Am Heart J 72: 721-724, 1966. S 329

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XIV. COMMENTARY ON US PUBLIC HEALTH PUBLICATIONS

After the text of this review article was completed, the seven volumes relating to "Smoking and Health" issued by the Surgeon General was examined. The pages relating to cardiovascular disease are reproduced on yellow paper and commentaries appear on the succeeding pages. It can be noted that there are differences in interpretation of the state of knowledge at the time the Surgeon General's Reports appeared in 1964, 1967, 1968, 1969, 1971, 1972, and 1973.

		Commentary starts on page
1964	The Health Consequence of Smoking pp. 315-334	348
1967	Smoking and Health pp. 45-86	356
1968	Smoking and Health pp. 15-61	372
1969	Smoking and Health pp. 9-134	394
1971	Smoking and Health pp. 15-134	405
1972	Smoking and Health pp. 11-34	460
1973	Smoking and Health (draft available)	471

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SMOKING *and* HEALTH

REPORT OF THE ADVISORY COMMITTEE
TO THE SURGEON GENERAL
OF THE PUBLIC HEALTH SERVICE

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service

Chapter 11

Cardiovascular Diseases

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SMOKING AND NON-CORONARY CARDIOVASCULAR DISEASE	325
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Chapter 11

INTRODUCTION

It has been suggested repeatedly that smoking may have adverse effects on the cardiovascular system. Recently, studies of large groups of people have shown that cigarette smokers in particular are more prone to die early of certain cardiovascular disorders than non-smokers. Chief among these disorders is coronary artery disease, and the present chapter deals mostly with this subject. The chapter begins with a summary of information about the acute effects of smoking on the cardiovascular system. This is followed by a brief account of coronary disease, its frequency in different kinds of people, and the many factors known or thought to affect the likelihood of its development. The aim here is not to review critically our knowledge of coronary disease but only to give background for what follows. Next is summarized the information currently available from study of large population groups on the association of cigarette smoking with an increased tendency to have coronary disease. There follows a brief discussion of smoking and non-coronary cardiovascular disease. Finally, there is a short review of evidence relating to the question of whether cigarette smokers may, as a group, differ from non-smokers in ways not caused by smoking itself. Mortality ratios showing the association between cigarette smoking and deaths from cardiovascular disease, especially coronary disease, do not indicate the magnitude of the burden. This can be better appreciated from consideration of the following facts: cardiovascular disease deaths now total more than 700,000 annually in the United States. Of these more than 660,000 were due to heart disease, with more than 560,000 due to arteriosclerotic heart disease including coronary disease. The remaining approximately 40,000 were ascribed to disease of other parts of the cardiovascular system. Deaths from lung cancer total approximately 30,000. A mortality ratio of 1.7 for coronary heart disease among cigarette smokers in the seven prospective studies represents from 32.9 percent to 51.7 percent of all excess deaths, whereas the much higher lung cancer mortality ratio of 10.8 from the same studies represents only 13.5 percent to 21.0 percent of total excess deaths (Chapter 8, Tables 19, 25).

PERTINENT PHARMACOLOGY

The acute cardiovascular effects of smoking in man and experimental animals are like those caused by nicotine alone. A smoker who inhales gets usually 1–2 mg of nicotine from a cigarette (56, 57).

Low concentrations of nicotine stimulate sympathetic ganglia, and high concentrations paralyze them. Parasympathetic ganglia respond in the same way but are less sensitive. Nicotine can also have a sympathomimetic effect by causing the discharge of norepinephrine and epinephrine from chromaffin cells in various tissues, including heart, vessels, and skin (9, 10, 11). In addition, nicotine produces effects reflexly by stimulating the chemoreceptors of the carotid and aortic bodies. When nicotine is given intravenously in increasing doses to dogs or cats the first effects, at about 1 microgram/kg body weight, are increased breathing and sympathetic stimulation, with predominant vasoconstriction, cardiac acceleration, and rise in blood pressure, resulting from stimulation of the aortic and carotid bodies (17). Doses of 4 to 8 micrograms/kg can stimulate pulmonary and coronary chemoreflexes which produce opposite effects. If all these receptors are inactivated, much higher doses are needed to evoke the cardiovascular effects of sympathetic stimulation, presumably through action on sympathetic ganglia or chromaffin tissue. Intravenous administration of nicotine in the experimental animal causes a discharge of epinephrine from the adrenal medulla, and in man heavy cigarette smoking produces an increased urinary excretion of catecholamines (84, 99).

Smoking 1–2 cigarettes causes in most persons, both smokers and non-smokers, an increase in resting heart rate of 15–25 beats per minute, a rise in blood pressure of 10–20 mmHg systolic and 5–15 mmHg diastolic (76, 78, 85, 86), and an increase in cardiac output of about 0.5 l/min/sq.m (75). There is a decrease in digital blood flow and a consequent drop in finger and toe temperature (31, 78, 103). The decrease in peripheral blood flow which normally follows smoking does not occur in a sympathectomized limb, indicating that the effect is mediated primarily by the sympathetic nervous system rather than through the release of catecholamines from other sites or the direct effect of nicotine upon the smooth muscle of the blood vessels themselves (103). Intravenous nicotine, and probably cigarette smoking as well, can produce a slight transitory increase in the blood flow to resting calf muscle (79).

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This section on pharmacology of nicotine is so brief that it does not do justice to the considerable amount of information available in 1964. The opening paragraph cites (57) Larson, Haig and Silvette (1961) which is the most extensive monograph on Tobacco. The cardiovascular effects of nicotine are discussed in pages 14 to 232, and the relation of tobacco to cardiovascular disease in pages 653 to 686. However, the monograph is mentioned only in reference to the amount of nicotine absorbed.

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In the dog, nicotine and cigarette smoke cause an increase in coronary flow as the blood pressure, cardiac output, and heart work increase (30, 53). These effects resemble those of epinephrine. Nicotine has been found to cause a transient decrease in cardiac oxygen utilization followed by a slight increase (53). Relatively little information is available about the effect of smoking on coronary blood flow in man. In normal subjects it is reported that cigarette smoking produces an early increase in coronary flow as heart work increases, but there is little change in oxygen utilization by the myocardium (2). With continued "steady state" smoking the coronary flow and cardiac oxygen utilization are maintained at the resting level in both normal subjects and persons with coronary heart disease, despite increased blood pressure, heart rate, and heart work (74). A larger experience must be gathered in this field before statements about the acute effects of smoking on the human coronary circulation can be made with assurance. The atherosclerotic rabbit heart, like the normal rabbit heart, shows an initial drop in coronary flow on administration of nicotine, but demonstrates less of a subsequent increase above the resting level than does the normal heart (97). These effects are said to be equivalent to those produced by norepinephrine in doses one-tenth as large as the nicotine dose.

Little or no change in the electrocardiogram of most normal persons or cardiac patients, except for an increase in rate, is produced by smoking or by the intravenous injection of an equivalent dose of nicotine (82, 93). In some persons there is a slight depression of the S–T segment and a flattening of 1–2 mm in the T wave of the limb leads. These changes are not like those associated with myocardial ischemia. Rarely in persons with true angina, an attack of pain is precipitated by smoking. An ill-defined syndrome consisting of chest pain, palpitation, and shortness of breath, known as "tobacco angina", has been described as occurring in smokers who do not have organic heart disease, but it is rarely diagnosed today (73, 82). Extrasystoles and other cardiac arrhythmias have been reported to be caused by smoking, but such cases appear to be unusual.

The ballistocardiogram obtained from a high-frequency table is sometimes changed by smoking a cigarette from a normal pattern to one said to be typical of coronary disease (78, 91). This phenomenon is rare in healthy persons below 50, becomes increasingly common with advancing years in apparently healthy persons, but is particularly prone to occur at any age in persons with actual coronary disease. The effect has been used as a "stress test" to help uncover coronary disease, but false positive and negative results are common. The ballistocardiographic changes on smoking have been variously interpreted as resulting from impaired myocardial contractility (78), from changes in the peripheral circulation (82), or from uncertain causes related to the physical properties of the high-frequency table as well as changes in the circulation.

Cigarette smoking causes an increase in the concentration of serum-free fatty acids in man (59), apparently mediated by stimulation of the sympathetic nervous system (51). Although continued administration of epinephrine to dogs over many hours can produce substantial increases in serum cholesterol, phospholipids, and triglycerides, such an effect has not yet been reported from nicotine or tobacco smoke (48, 92).

The clotting time of the blood can be decreased 50 percent or more in experimental animals by stimulation of the sympathetic nervous system or by administration of epinephrine (12, 13, 14), but attempts to demonstrate that cigarette smoking alters the clotting properties of the blood in man have been unsuccessful (5, 63). A decrease in platelet survival *in vivo* has been found after smoking (63). Cigarette smokers have been reported to show substantial decreases in hematocrit, hemoglobin, and platelet counts after abstinence of 1–2 weeks (25), but hemoglobin concentrations are alike in smokers and non-smokers of the same population group (64).

Attempts have been made to induce atherosclerosis in rats by the chronic administration of nicotine for periods up to a year without success (93).

Tobacco has antigenic properties (29, 43). Rats can be sensitized to tobacco extracts by intraperitoneal injection. Over a third of smokers demonstrate a positive "immediate" skin reaction to such extracts while only about 10% of non-smokers are said to give positive tests. The presence of serum reagins in persons with positive skin tests has been demonstrated by passive transfer techniques. Persons with thromboangiitis obliterans and smokers with occlusive vascular disease of other types are said to show a much higher incidence of positive skin tests than healthy smokers. The cardiovascular diseases which have been related to smoking, however, do not in general resemble those usually ascribed to an immune mechanism.

In man and experimental animals smoking or the injection of nicotine causes increased secretion of antidiuretic hormone. The renal effects of this are easily demonstrable but the quantity of hormone secreted in response to smoking is probably too small to have significant vascular effects (17).

In summary, the acute cardiovascular effects of smoking and of nicotine closely resemble those of sympathetic stimulation, and to a considerable extent are mediated by excitation of the sympathetic nervous system. No additional or unique cardiovascular effects have been demonstrated which, in the light of our present understanding, seem likely to account for the observed association of cigarette smoking with an increased incidence of coronary disease.

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The information on the effect of smoking on coronary blood flow in man was sufficient to show that there was no harmful influence. The conclusions of (2) Bargeron et al., 1957 and (74) Regan et al., 1961 were similar to those obtained by six groups of investigators administering nicotine in dogs (see page 270). At the time Bargerson et al. and Regan et al. 1961 completed their experiments, their conclusions were accepted because the nitrous oxide technique was the only means of measuring coronary blood flow and myocardial metabolism in man. The observations by Regan et al 1961 have not been disproven by subsequent reports. The Discussion quoted from the article is as follows:

Discussion

The experimental conditions of this stu were limited to evaluation of the sustain effects of cigarette smoking upon the m cardium of man after the peripheral he dynamic changes had become well establish Consequently, interpretation of the data ca not be applied without reservation to t acute changes occurring immediately af the onset of smoking, which may well be qualitatively different.[6] If one assumes, however, that nicotine is the principal pharmacologic agent in tobacco smoke, then the effects of intracoronary infusion of this substance are of some interest. In the intact dog it has not been found to modify coronary blood flow when injected into the anterior descending artery, despite substantial increase in myocardial contractility.[9] Left coronary perfusion with nicotine also has failed to increase flow in the atherosclerotic rabbit heart, despite cardiac acceleration and enhanced contractility.[10] These studies, in which different methods of determining coronary flow have been employed, tend to reduce the possibility that these results in man represent an artifact of the nitrous oxide method.

Augmentation of coronary blood flow may usually be anticipated when there is an increase in heart rate, systemic arterial pressure, cardiac output, and left ventricular work. In this manner, the apparently greater oxygen requirement of the myocardium would be severed. Failure to find such increases of myocardial blood flow and oxygen consumption in the coronary subjects during cigarette smoking may plausibly be related to the "fixed coronary resistance" alleged to exist in such patients.[11] That the abnormal coronary vasculature is not responsible becomes apparent from the similar response in the subjects without evidence of coronary disease. In view of the evidence that ventricular contraction acts to impede coronary flow within the left ventricular wall,[12] the enhanced ventricular contractility as reflected by left heart work may have produced such an effect. This view is difficult to accept, since the failure of coronary flow to meet the need for greater oxygen usage should be associated with augmented oxygen extraction.

Although many of the effects of smoking and nicotine infusion mimic those of catecholamine administration,[5] an evaluation of endogenous catechols in plasma in response to smoking too small to affect the coronary vasculature appears unlikely. On the contrary, small graded doses of catecholamine induce changes in coronary flow before increments in rate and pressure.[13] Another humoral agent possibly released during smoking is antidiuretic hormone.[5] Its potent coronary vasoconstrictor properties raise the possibility that any undesirable effects of smoking could be effected through its activity. Even though the plasma levels of vasopressin probably are not sufficient significantly to restrict coronary blood flow per se, the lack of increased flow despite increments of rate and pressure may represent a restrictive effect of low hormone concentration upon the response to these stimuli of coronary vasodilatation.

It would appear that an enhanced ratio of left ventricular work to oxygen uptake may be maintained for some time without cardiac dysfunction. Such is the case in animals with chronic complete heart block[14] or in those subjected to expansion of intravascular volume.[15] Such disproportion in coronary subjects, however, if large enough, could presumably produce ischemia symptoms. This circumstance, as suggested by this study, would appear to be an uncommon occurrence.[16]

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Tobacco angina. In 1963, Oram and Sowton reviewed the literature and his experiences on tobacco angina. Although the condition is rare, its occurrence has been ignored in prospective and clinical studies of angina pectoris. The subject is discussed in pages 15 to 18. Since the article does not appear in the 1964 or subsequent reports, the summary is reproduced below:

Summary

The term tobacco angina as previously used has become meaningless, and covers at least five separate syndromes to which we have drawn attention. A definition of tobacco angina is offered.

Angina as a result of smoking is a real entity, but rare. Including our three patients, only 17 convincing examples, confirmed electrocardiographically, have been recorded. The commonest type occurs in patients who already have typical Heberden's angina due to coronary disease and precipitated by the more usual causes. A very rare type is that occurring in apparently healthy young people in whom electrocardiographic changes characteristic of coronary insufficiency appear within a few seconds of smoking a cigarette, accompanied or unaccompanied by cardiac pain, but in whom the electrocardiographic changes and pain are said not to be induced by other causes such as exertion, emotion, and cold. We feel it is likely that follow-up studies of these rare patients might later reveal coronary disease.

It is important when searching for patients suffering from tobacco angina to investigate them not only while they are smoking, but after smoking followed by exercise, and after exercise followed by smoking, otherwise examples will be missed. Of 309 smokers with angina questioned concerning the possible role of cigarette smoking in causing cardiac pain, 20 claimed to have angina on smoking. These were re-examined clinically, and electrocardiograms were taken at rest, after smoking, after smoking followed by exercise, and after exercise followed by smoking. Only two examples of genuine tobacco angina were found by this means.

Our three patients had ischaemic heart disease with chest pain, and electrocardiographic evidence of coronary insufficiency was produced by exercise and by smoking cigarettes or cigars. No significant change in blood-pressure accompanied the cardiac pain and electrocardiographic changes which resulted from smoking. These effects induced by smoking were invariably accompanied by tachycardia, but were not secondary to tachycardia as induced by intravenous atropine.

Neither smoking herbal cigarettes nor the intravenous injection of normal saline induced angina or electrocardiographic changes.

The most satisfactory explanation of the cardiac pain and electrocardiographic changes appears to be that nicotine gives rise to coronary insufficiency not by coronary vasoconstriction as previously supposed but by coronary vasodilatation. In spite of this vasodilatation the blood supply to the myocardium becomes insufficient because of the concomitant increase in cardiac work, resulting from an increased cardiac rate, rise in blood-pressure, or both. Possibly also the liberation of catechol amines has a deleterious effect on the metabolism of the myocardium.

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It is important when searching for patients suffering from tobacco angina to investigate them not only while they are smoking, but after smoking followed by exercise, and after exercise followed by smoking, otherwise examples will be missed. Of 309 smokers with angina questioned concerning the possible role of cigarette smoking in causing cardiac pain, 20 claimed to have angina on smoking. These were re-examined clinically, and electrocardiograms were taken at rest, after smoking, after smoking followed by exercise, and after exercise followed by smoking. Only two examples of genuine tobacco angina were found by this means.

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The vasodilatation results from liberation of catechol amines from stores in or near the blood-vessel walls, including the chromaffin tissue along the coronary vessels themselves. Catechol amines cannot be liberated as a result of stimulation of sympathetic ganglia by nicotine, as the blood level of nicotine attained by smoking is too low for this purpose. It is, however, sufficient to liberate catechol amines from blood-vessel walls.

The explanation of the rarity of tobacco angina is not clear. Presumably a few individuals are in some way hypersensitive. The investigation of skin sensitivity to tobacco should be made by using fractionated extracts of tobacco smoke rather than extracts of tobacco itself. We have been unable to demonstrate any sensitivity to either.

To test the theory that release of catechol amines by nicotine leads to tobacco angina, we tried six drugs which might be expected to block the nicotine effect, and four which might be expected to aggravate it. The former group consisted of dihydroergotamine, antiserotonin, reserpine, hydrocortisone, guanethidine, and methyl dopa, while the latter comprised serotonin and three monoamine oxidase inhibitors. The results are given in detail. Surprisingly, the monoamine oxidase inhibitors had a protective effect in all three patients. None of these drugs blocked the effect of exercise.

Our results support the belief, previously based on animal experiments, that nicotine exerts an action like that of the sympathetic stimulants because it liberates noradrenaline.

If it is thought by the patient that his angina is induced more easily during the time he is smoking, he should be persuaded to abstain for one month, and the electrocardiogram should then be repeated. If clinical improvement is reported and the height of the T wave has also improved, he should be permanently discouraged from smoking.

Indiscriminate advice against smoking, as far as angina is concerned, is not justified, and each patient needs individual assessment.

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GENERAL OBSERVATIONS ON CORONARY HEART DISEASE

Heart disease is the most common cause of death in our population, and coronary disease is the commonest variety of fatal heart disease (59). In 1961 there were 1,501,522 deaths from all causes in the United States. Heart disease deaths numbered 663,391 of which 502,351 were due to arteriosclerotic heart disease.

The disorder consists of obstruction or narrowing of the coronary arteries, reducing the blood supply to the heart muscle. The underlying cause of the obstruction is coronary atherosclerosis, but an acute coronary artery occlusion is often caused by the formation of a blood clot in a diseased artery. The common manifestations of coronary disease are angina pectoris, recurrent brief attacks of chest pain caused by inadequate blood supply to the heart muscle; myocardial infarction, or necrosis of a portion of the heart muscle due to acute loss of blood supply; congestive heart failure, a chronic state caused by inability of the heart to pump enough blood to satisfy the demands of the body; and sudden death resulting from cardiac standstill or ventricular fibrillation.

There are considerable differences in the prevalence of coronary heart disease in different countries, and often in different ethnic and socio-economic groups within a particular country (49, 62). The reported death rate of arteriosclerotic heart disease, which is primarily coronary disease, is higher in the United States than in other countries. It is also quite high in New Zealand, Australia, South Africa, Canada, and Finland, and moderately high in Great Britain. The death rate in Norway, Sweden, and Denmark is roughly half that in the high death rate countries (65). The death rate in Japan appears to be about one-sixth that in the United States, although persons of Japanese origin living in the United States are said to have a death rate similar to that of the general population of this country (52).

Because of changing diagnostic skills and revisions in nomenclature of disease, it is difficult to be certain of the change in incidence of coronary disease in the United States over the past few decades, but there is a general opinion that the incidence is increasing in this country and in England, particularly in the younger male group (59, 62, 65, 83). In 1955 the mortality rate from arteriosclerotic heart disease was reported to be about 240 per 100,000. Although this is an increase of more than 50% over the rate in 1940, it has been estimated that less than 15% of the increase represented a real change in incidence of the disease, the remainder depending upon changes in diagnosis, in nomenclature and in the age of the population (59). Since 1955 the death rate from coronary disease (ISC 420) and from arteriosclerotic and degenerative heart disease (ISC 420 and 422) has continued to increase gradually. In 1960 the age-adjusted death rate from 420 and 422 was 336 per 100,000 for white males and 160 for white females (55).

Although the basic cause or causes of coronary heart disease are obscure, certain factors other than smoking are known or thought to predispose to the condition or to be associated with an increased incidence.

The incidence of coronary heart disease in men under 45 is about 5 times as great as that in women (Table 1) (15, 20, 59, 62). In both sexes the incidence increases with advancing years. After the menopause the incidence increases rapidly in women, and at age 80 the death rates from coronary disease are about the same for the two sexes. Coronary thrombosis plays a relatively more important role in precipitating myocardial infarction in young men than it does in old men (105). In studies of large population groups coronary disease has been associated with elevation of the serum cholesterol, hypertension, and marked overweight (19, 20, 24, 36, 45, 59, 62).

Some individual characteristics have been said to be associated with coronary disease. There is a significant familial tendency to develop it (36, 69, 81, 96). Persons with a mesomorphic constitution are said to be more vulnerable than endomorphs and ectomorphs (59, 62, 83). A coronary-prone personality has been described as the aggressive, competitive person who takes on too many jobs, fights deadlines, and is obsessed by the lack of adequate time for the performance of his work (33, 34, 35).

TABLE 1.—*Death rates per 100,000 from arteriosclerotic and degenerative heart disease* by sex and age, United States, 1958–60*

Age Group	Males	Females	Both Sexes
Under 35	3.3	1.2	2.2
35–44	90.2	18.3	53.3
45–54	353.7	79.8	213.5
55–64	928.5	314.5	610.2
65–74	2129.2	1062.0	1569.5
75 or over	4765.1	3738.4	4179.7

*Includes ISC numbers 420 and 422.

Source: WHO Epidemiological and Vital Statistics Report, Vol. 16, No. 2, 1963 (15).

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Some of the articles cited in this page discuss the interrelationship between smoking and other risk factors. One example is (81) Russek and Zohman, who described hereditary predisposition as well as other risk factors in coronary heart disease of young adults. Although smoking was prevalent in the coronary group, it appeared to the authors to be an indication of heightened emotional tension rather than a predisposing or causative factor in coronary heart disease.

TOBACCO. Prior to the attack, 90% of the coronary patients indulged regularly in the use of tobacco, while 10% were either nonsmokers or participated on rare occasions. Among controls, on the other hand, 62% were habituated while 38% smoked occasionally or not at all. Heavy smokers were also found to be far more frequent in the coronary group. Thus, 70% of their number had smoked at least 30 cigarets per day prior to their attack as compared with only 35% in the contratest group. These observations indicate, therefore, that smoking was not only more prevalent in the coronary group but also that the coronary patients who had smoked were more heavily addicted to the use of tobacco. Nevertheless, it is not clear from these findings whether nicotine is a predisposing factor in coronary heart disease or whether its more frequent and excessive use among young candidates is merely a reflection of the heightened emotional tension so prevalent among them.

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Certain occupations have been said particularly to favor the development of coronary disease, notably those which feature responsibility and stress (34, 81, 87), and which are sedentary in nature (71). Others (33, 72, 90) have not found that executives are more prone to coronary disease than non-executive personnel. Physicians have been said to have 3 or 4 times as much coronary disease as farmers or laborers (87), and general practitioners to have 3 times as much as dermatologists (80). Occupations involving much physical activity are said to be protective (66, 67, 77). City life has been said to be more closely associated with coronary disease than suburban life, and men who drove more than 12,000 miles a year seemed, in one study, more prone to the disease than those who drove less (64).

It has been widely held, and occasionally denied, that a diet high in saturated fat predisposes to the development of coronary disease (40, 52, 69, 81). A correlation between the national incidence of coronary disease and the percentage of food calories available as saturated fat has been reported among those countries for which adequate data exist (66). The serum cholesterol tends to rise when saturated fat is added to the diet, and it falls significantly when unsaturated fat is substituted (61). It has also been suggested that general over-nutrition, rather than excess saturated fat predisposes to coronary disease, on the grounds that the correlation of coronary disease with total available calories or sugar consumption per capita is as good as that for percentage of calories in fat (106).

In general, it is apparent that multiple personal and environmental factors can markedly affect the incidence of coronary disease.

SMOKING AND CORONARY HEART DISEASE

Over the last two decades a considerable number of epidemiologic studies on different populations, employing different techniques, have shown with remarkable consistency a significant relationship between cigarette smoking and an increased death rate from coronary heart disease in males, particularly during middle life. There has been little dissenting evidence. The association of coronary disease with the use of tobacco in other forms has not been striking. The documentation for these statements is given in the following paragraphs. Particularly important is the information in Chapter 8, Mortality.

English et al. (26) found the incidence of coronary disease in male patients at the Mayo Clinic about 3 times greater in cigarette smokers than in non-smokers in the 40–59 year age range, but found little relation to smoking above (8). Russek (81) reported a similar relationship, but less striking, in young men with coronary disease. Mills (64) in a study of reported mortality in a Cincinnati population found that heavy smokers in the 30–59 year age range had twice as high a death rate from coronary disease as non-smokers. Male Seventh Day Adventists, who are non-smokers, were found by Wynder and Lemon (104) in a study based on hospital admissions to have significantly less coronary disease and to develop it later in life than the general male hospital population. Haag and Hanmer (37) reported that employees in the tobacco industry, who tend to smoke heavily, had a lower death rate for cardiovascular disease than the general population in their geographic region, but no report was made of mortality rates within the tobacco-worker group, divided by smoking habits. The study has been criticized on this and other grounds (16).

Large-scale prospective studies of mortality in British physicians (Doll and Hill, 21), United States males 50–69 recruited by volunteer workers (Hammond and Horn, 38, 39, 40, 42) and V.A. Life Insurance policyholders (Dorn, 22) have confirmed the association of death from coronary disease with cigarette smoking. In the British study, a step-wise association was found between the amount of tobacco consumed (not entirely cigarettes) and the mortality from coronary disease. The association occurred in the 35–54 year age range, but not in older men. Hammond and Horn found a similar graded relationship between coronary deaths and cigarette smoking, the death rate being more than twice as great in men who smoked over a pack a day as in non-smokers. Men who had stopped smoking for more than a year at the start of the study had a coronary death rate lower than those who continued.

Studies on special groups of men, such as longshoremen (Buechley et al. 8) members of a fraternal order (Spain and Nathan, 83) and industrial employees (Paul et al. 71), which, in the latter two instances, incorporated clinical coronary disease, as well as coronary deaths, also have shown a relationship between coronary disease and smoking. The relationship was closer for men under 51 than for older men, and closer for myocardial infarcts and death than for angina pectoris (70, 83).

The long-term prospective studies of cardiovascular disease in Framingham (19) and in Albany (24) which have features of painstaking search at regular intervals for clinical manifestations of disease, have, on pooling the data (Doyle et al. 23) shown a three-fold increase in the incidence of myocardial infarction and coronary deaths in men who are heavy cigarette smokers as compared to non smokers, pipe and cigar smokers, and former cigarette smokers. In the pooled data the incidence of angina pectoris did not show a significant association with cigarette smoking. The lack of this particular relationship had been suggested on the basis of clinical experience (White and Sharber, 102).

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When selected groups are examined, there is no relationship between cigarette smoking and an increased death rate from coronary heart disease. The report by Cohen and Heimann (1962) is a good example. It is reproduced in its entirety.

Cohen J and Heimann R K: Heavy smokers with low mortality. Ind Med Surg 31: 115-120, 1962.

This paper extends mortality rates of cigarette division employees of The American Tobacco Company to cover the period 1957-1960. Previous mortality studies of the same population were made by Dorn and Baum of the National Institutes of Health, embracing October, 1946, through 1952,[1] and by Haag and Hanmer, for the years 1953 through 1956.[2] An intensive investigation of this population's smoking habits was made in 1956 by Finkner et al.[3] of the Institute of Statistics of the University of North Carolina.

The 1957-1960 data confirm the findings of Dorn-Baum and Haag-Hanmer that the age-, color-, and sex-adjusted mortality rate for all causes, for cancer, for respiratory cancer, and for cardiovascular disease in this population are average or lower than average when compared with the general population rates.

The significance of this finding relates to the determinations of Finkner et al.,[3] who found that the population under study had a markedly higher percentage of regular cigarette smokers than the general U. S. population. Finkner's study also indicated that the percentage of these factory employees consuming upwards of 20 cigarettes daily was twice that in the general population.

This series of studies thus establishes a distinctly heavier-than-average smoking population which has, over a period of 14¼ years, manifested fewer deaths of all kinds, and fewer deaths from cancer, lung cancer, and heart disease, than the expectancy for an average population of its age, sex, and racial composition. These results are in direct opposition to the hypothesis that cigarette smoking per se causes higher mortality rates generally and for lung cancer and/or heart disease.

The three consecutive longevity investigations covered 70,532, 45,455 and 41,967 person-years respectively, or a total of 157,954. The average size of the population during the 171 months under study was slightly over 11,000.

Mortality Rates for 1957 through 1960

Table I compares the observed deaths in the population studied with the expected number based on age-sex-color-specific death rates for the general U. S. population. This table and the method of its calculation are patterned after those published by Dorn-Baum and Haag-Hanmer.

TABLE I.
OBSERVED AND EXPECTED NUMBER OF DEATHS FROM SPECIFIED CAUSES AMONG FULL-TIME AND RETIRED EMPLOYEES OF CIGARETTE PLANTS AND STEMMERIES OF THE AMERICAN TOBACCO COMPANY
JANUARY 1957 — DECEMBER 1960

Cause	Expected No. of Deaths	Observed No. of Deaths	Observed to Expected
All causes	425	325	76%
Cancer — all forms (140-205)	75	47	63%
Cancer — respiratory system (160-164)	14	6	43%
Cancer of bronchus and trachea, and of lung specified as primary (162)	7	0	0
Cardiovascular (400-468)	180	154	86%
Coronary disease (420)	116	100	86%

NOTE: Numbers in parentheses are cause-of-death categories of Seventh Revision of The International List, as used in *Vital Statistics of The U. S.*

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Table I indicates that the observed number of deaths during the 1957-1960 period was 76% of the number that would be expected to occur in an average U. S. population similarly stratified as to age, sex, and color. The number of cancer deaths was 63% of the expectancy. Respiratory cancer deaths were 43% of the expectancy, cardiovascular deaths 86% of the expectancy, and coronary deaths 86% of the expectancy. No deaths from primary lung cancer occurred during this period, although an expectancy of seven such deaths was derived from vital statistics for the U. S. as a whole.

Previous Mortality Rates for the Same Population

Similar percentages of observed-to-expected deaths in the several classifications were observed by Dorn-Baum for the period October 1946-1952 and by Haag-Hanmer for 1953-1956. Percentages of observed-to-expected deaths covering the results of all three studies as well as the complete time span of 14¼ years are arrayed in Table II. Allowing for the random fluctuation in the number of particular causes of death that is observed in most population subgroups, and especially for those causes from which the number of deaths is small (e.g., respiratory cancer), the results of the three investigations show internal consistency. Except for the aforementioned cause involving few deaths, the percentages from one study to the next show no radical variation. The over-all percentages in Column 4, Table II, characterizing the observed-to-expected ratio for the several cause categories during the entire 14¼ year period, fall within a range of nine percentage points. Observed deaths ranged from 70% to 79% of the expectancy for all causes, for cancer, for respiratory cancer, for cardiovascular and for coronary disease.

Since Dorn-Baum did not compute a separate expectancy category for primary lung cancer as distinct from the general category of respiratory cancer both primary and secondary, this category does not appear in Table II. In the two latter studies covering eight years, four deaths from this cause were recorded, representing 36% of the normal expectancy of 11.

TABLE II.
PERCENTAGE OF OBSERVED TO EXPECTED DEATHS IN THREE SUCCESSIVE STUDIES OF FULL-TIME AND RETIRED EMPLOYEES OF CIGARETTE PLANTS AND STEMMERIES OF THE AMERICAN TOBACCO COMPANY

	Dorn-Baum (Oct. 1946-1952)	Haag-Hanmer (1953-1956)	(1957-1960)	Total Period (Oct. 1946-1960)
All causes	88%	69%	76%	71%
Cancer - all forms	73%	77%	63%	70%
Cancer - respiratory system	86%	100%	43%	71%
Cardiovascular	65%	76%	86%	75%
Coronary disease	80%	65%	86%	79%

Smoking Habits of the Population under Study

As previously reported by Finkner et al., the proportion of regular cigarette smokers among the tobacco employees studied was much greater than that in the general U. S. population. Among white males, 77.2% of the tobacco employees were regular cigarette smokers, compared with 49.9% for the general U. S. population; for nonwhite males, 84.1% compared with 48.4%; for white females, 44.4% compared with 23.6%; and for nonwhite females, 61.7% compared with 22.9%.

The tobacco employee population also included a considerably higher percentage of smokers consuming more than 20 cigarettes daily than the general U. S. population. Among white males, 32.8% of the tobacco employees smoked more than 20 cigarettes a day as against 13.3% for the general U. S. population. Nonwhite males among the tobacco employees included 16.5% smoking more than 20 cigarettes a day as against 6.9% in the general U. S. population. For white females the proportion was 6.9% among tobacco employees as against 2.1% in the general population, and for nonwhite females 4.0% as against 1.7%. In each category, the proportion of tobacco workers smoking more than 20 cigarettes a day is of the order of two and a half times that of the comparable segment of the U. S. population.

Methodology

In all three mortality studies, observed deaths were tabulated from reports of the Metropolitan Life Insurance Company, which underwrites insurance policies on all employees of the group studied, including those on leave, those retired for disability, and those retired for age. Death rates for the general U. S. population were computed by dividing total deaths, as reported in *Vital Statistics of the U. S., Volume II*,[4] by the population estimates issued by the Bureau of the Census for July 1 of each year (Series P-25).[5]

For the 1957-1960 period, rates for the year 1958 were used to compute expectancies for 1957 and 1958, and rates for the year 1959 were used to compute expectancies for 1959 and 1960. Rates were computed separately for male white, male nonwhite, female white, and female nonwhite, and for all the age groups 15-24, 25-34, 35-44, 45-54, 55-64, 65-74, 75 and over. These rates were applied to the number of person-years of exposure in each age, color, and sex category of the population under study. The roster of employees (including retired employees and those

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on leave) was taken as of July 1 in each year. Expectancies throughout were calculated for each single year and summed for the period studied.

Measurement of the subject population's smoking habits by Finkner et al. was methodologically similar. Independent investigators recorded individual smoking histories and classified them by age, sex, color, and rate of cigarette consumption. These were ranged against the corresponding findings for the general population of the U. S. by subgroup, as reported by Haenszel, Shimkin, and Miller of the U. S. Department of Health, Education and Welfare,[6] based on a Census Bureau study.

The above procedure follows that of Haag and Hanmer, who compared employee smoking habits with those of the U. S. population, and employee mortality rates with those of the U. S. population, both stratified by age, sex, and color.

No sampling or estimating was involved in any of these studies. Smoking habits were measured by applying pretested procedures individually to virtually every member of the population under study (98.1%). Data on age, color, sex, and mortality were available for each individual member of the population and were summed as above described.

Characteristics of the Population

The population under study was that defined by Dorn and Baum of the National Institutes of Health. It consists of full-time employees in factories and leaf departments of The American Tobacco Company in Virginia, North Carolina, and Kentucky. Turnover in this employee group is negligible. On July 1, 1960, approximately 66% of the population had service records of ten years or more, and 20% had service records of 25 years or more. On August 1, 1953, 48% had been employed ten or more years, and 10%, 25 or more years.

As reported by Dorn and Baum, employees who are unable to work eventually are carried on the payroll as on leave without pay but remain covered by insurance so that they remain part of the population for purposes of these studies. Retired employees retain insurance coverage and also are included.

Thus the population is a coherent group for purposes of mortality investigation. The degree of this coherence is indicated by its average age, which increased almost precisely three years between July 1, 1957, and July 1, 1960 — from 42.8 years to 45.7 years, respectively.

White males accounted for 43% to 46% of the population during this period, these percentages being minimum and maximum. Males white and nonwhite accounted for 57% to 61% of the subject population. Men over 45 accounted for 31% of the employee group on July 1, 1960.

Comment

The health history of this population of heavy-smoking tobacco company employees tends to disprove the hypothesis that cigarette smoking causes higher mortality from all causes, from cancer, from lung cancer, or from heart disease. This interpretation is strengthened by the following data of observation:

1. The substantial degree to which the studied population's cigarette consumption exceeds the national average: In the percentage smoking more than 20 cigarettes daily, the Finkner study group recorded the ratio as 2:1 or more in every subgroup and in virtually every age group. In view of the population's vocational interest in the product it manufactures, and the provision of a free package of cigarettes each working day, this characteristic of the group studied is not astonishing.

2. The unusually stable nature of this employee group, as indicated under "Characteristics of the Population" above: Stability of the population for purposes of these studies is also insured by the fact that employees on leave, retired for disability, or retired for age, continue to be covered under the group insurance plan. These employees or former employees were included on the July 1 rosters used to compute expected deaths; and actual deaths among them were reported by the Metropolitan Life Insurance Company.

3. The extended nature of the mortality research, covering a continuous time span of 14¼ years.

4. The consistently lower-than-average mortality of the studied population for each of the three mortality studies (Table II).

5. The consistency of the degree to which this mortality for the entire 14¼ year period is lower than the national rate, as between the various causes of deaths (Table II, Column 4).

Other Statistical Studies

A number of studies, of which those of Doll-Hill[7] and Hammond-Horn[8] are representative, have yielded a statistical association in individuals between cigarette smoking and higher mortality rates. Other studies, including Eastcott, Dean, and the present study, have shown no such association. A number of distinctions may be noted in connection with the diametric opposition between the results of the two groups of studies.

Statistical association studies of the Ham-

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mond-Horn, Doll-Hill type compute expected deaths on the basis of mortality rates shown by professed nonsmokers. The professed nonsmoker is taken as the norm or "average" against which various types of smokers are compared. This raises two questions: (1) whether those smokers who manifest higher mortality rates do so as a direct result of the effects of smoking, or whether the smoking habits of some of these higher-mortality smokers are diagnostic of other factors that predispose to shorter life, and (2) whether the professed nonsmoker with his low mortality rate can be taken as a norm.

The former question cannot be answered from the statistics themselves, since this would require that all relevant or predisposing factors other than smoking be held constant. No attempt was made in the Doll-Hill, Hammond-Horn, or their counterpart studies to do this, since all relevant factors affecting mortality and or cancer mortality are not known, and since some of the suspected factors — previous medical history, genotypic differences, constitutional predisposition, exposure to various environmental agents, "rate of living," the "stress" factor, etc. — are difficult if not impossible to reduce to mathematical terms, even if they could be gathered for populations large enough for statistical study.

Touching on the latter question, Berkson[9] has noted that

> . . . persons who are nonsmokers, or relatively light smokers, are of a constitutional type that is biologically disposed to self-protective habits. . . . It is not implausible that they should be, on the average, relatively longevous, and this implies that the death rates generally in this segment of the population will be relatively low.

The extent of this difference between death rates of professed nonsmokers and average U. S. citizens was indicated by Hammond-Horn, who computed mortality rates of 777, 1,253, 1,781, and 3,280 per 100,000 for nonsmoking white males in their 50-54, 55-59, 60-64 and 65-69 age groups, compared with rates of 1,469, 2,210, 3,402, and 4,895 per 100,000 for white males of the same age groups in the general population. These mortality differences between the professed nonsmoker and the "average" white male reported by Hammond-Horn were great — 85%, 76%, 91%, and 49%. Should Berkson's characterization of nonsmokers be correct even for a number of persons in that category, the Hammond-Horn interpretation that cigarette smokers incur "excess" mortality rates becomes meaningless. That is, the association their data showed reflects only the choice of an abnormally longevous group as a criterion of what is "normal." The same would be true of a number of other statistical association studies patterned on the Doll-Hill model.

The influence of this choice of criterion on their final calculations is evident from Hammond-Horn's own comparison of death rates among their "heavy cigarette smokers" with death rates among U. S. white males generally. In a 20-month period these rates were 1,222; 2,140; 2,707; and 3,856 per 100,000 for "heavy cigarette smokers" against 1,288; 2,096; 2,991; and 4,354 per 100,000 for U. S. white males in the four age groups. These rates hardly differ. In a subsequent 24-month period the "heavy cigarette smokers" showed slightly higher death rates than the U. S. average.

Apart from the question whether nonsmokers constitute a valid criterion of "normal" mortality — and Hammond-Horn's figures strikingly suggest they do not — a basic difference exists between the two types of studies mentioned. Those patterned after the Doll-Hill model (including Hammond-Horn) attempt a correlation between mortality rates and smoking habits in individuals. This requires the assumption that no unmeasured other factors exist that might account for or explain any correlation that is found. The number of such factors investigated, alone or in conjunction with smoking habits, is thus far small — the so-called "urban factor" (assumed by some to be air pollution), certain special occupational exposures, and alcohol consumption.

By contrast, studies of population subgroups including this series, those by Eastcott,[10] and that by Dean,[11] deal with mortality rates and smoking habits of groups. Dean compared native white male South Africans with British male immigrants to South Africa 45-64 years of age. Between 1947 and 1956 the death rate from lung cancer among the former was 50 per 100,000, and among the latter, 112. At the same time, white South Africans are among the world's heaviest cigarette consumers, with a per capita usage reported 68% above that in the United Kingdom in 1950 and 40% higher than the U. K. figure in 1955. Dean found urban residence to correlate with lung cancer incidence among South African whites, and concluded that "bronchial carcinoma must result from the total effect of genetic and environmental factors."*

*Dean later gathered smoking habit data for about half the lung cancer deaths in his study. Using these and a set of matched "controls" — deaths from other causes — he estimated mortality rates by age groups, by country of origin, by rural-urban residence, by occupational air pollution, and by rate of smoking.

The greatest relative association with lung cancer in these estimates involved country of origin (U.K. vs. Union of South Africa), but urban residence also showed consistent association. Occupation showed no association. As to smoking, rural South

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Eastcott found a parallel difference in lung cancer mortality between immigrants from Great Britain to New Zealand and native-born New Zealanders; at the same time tobacco consumption for the two groups was observed to be comparable. Eastcott concluded that "Differences in habits of tobacco-smoking are unlikely to contribute to this picture," and "The environmental factors concerned are unlikely too to be of a personal kind related to the way of life of the immigrant." In 1960, his data were extended to cover ten years' comparison of the mortality experience of 250,000 immigrants from the U. K. against that of 2,800,000 native-born New Zealanders.

Neither Dean nor Eastcott nor the present study offers a correlation between a single factor and mortality rates. They merely indicate that the higher mortality, whether from lung cancer alone or from this and other causes, does not associate with higher tobacco consumption. Rigorous interpretation of these findings as opposing the tobacco theory does not require the assumption that other factors remained constant. Actually, the results indicated that other factors did not remain constant, since important death rate differences were recorded despite similar or contrahypothetical rates of smoking, although the precise identification of these other factors is not germane to this inquiry.

Bearing on both types of study is the observed tendency of many selected population subgroups to manifest lower mortality rates than the population as a whole. Hammond-Horn, for example, estimated that "the death rate of our study population would stabilize at about 81% to 85% of the rate for white males in the general United States population," attributing this favorable comparison to selection of subjects from counties with lower death rates and to "a slight degree of socioeconomic selection."

Employee populations, such as the one studied by Dorn-Baum, Haag-Hammer and the writers, also represent a degree of selection resulting from the initial medical "screening" of applicants for employment. This effect, according to Hammond-Horn, "diminishes rapidly with time, is relatively slight after the third year, and for all practical purposes wears off within five years." Although the exact duration of this screening effect would not be important in a study extending 14¼ years, the significance of the present study does not lie in the fact that the tobacco employee population (like other selected groups) shows lower-than-average mortality. Rather, it lies in the fact that this lower-than-average mortality exists concurrent with a pattern of distinctly heavy smoking and in the fact that respiratory cancer mortality — alleged to be specifically and causally linked to cigarette consumption — is as much below average in this heavy-smoking population as is mortality from other causes or from all causes.

It has been pointed out that employee groups enjoy better-than-average medical care and for this reason are likely to manifest lower-than-average mortality rates. In the first mortality study in this series, Dorn-Baum noted the findings "are not surprising in view of the medical care program provided by the company for its employees." To the extent that medical care favorably affects the mortality rates of the employee population, the postulate is denied that cigarette smoking in and of itself is a major cause of respiratory cancer, or heart disease, or decreased longevity.

The previous study in this series[2] was criticized on several grounds by Case[12] who, in turn, was quoted by Cornfield et al.[13] This criticism if valid, also would apply to the present report:

1. Case questions the comparability of the tobacco workers with the general population in regard to characteristics other than smoking (and age-sex-color, which is allowed for in the determination of expected rates). On grounds such as these all statistical studies in this area may be called into question, but the present study less than most, since it represents a cross-sectional population with regard to socioeconomic-occupational levels. Further, the basis of Case's argument, that mortality, particularly from primary lung cancer, is associated with *other* factors, calls into question the specificity of the tobacco hypothesis.

2. Case applies a Hammond-Horn factor for increased lung cancer mortality expectation (based on the tobacco workers' greater smoking rate) of 1.7 to the previous study and arrives at an expected number of lung cancer deaths of seven. He then demonstrates that the sampling error of this study is such that 0-8 such deaths could occur at the $P = .05$ level, and that since this includes the adjusted frequency of seven, the results cannot refute the

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African-born men smoking 1-20 cigarettes a day showed lower lung cancer mortality rates than nonsmokers in such U.K. locations as Liverpool, Lancashire, Denbigh S.E., Flint and Cheshire. Also, "In South African rural areas the lung cancer mortality rate for men aged 45 to 64 years was very low for both nonsmokers and moderate smokers, and increased only with heavy cigarette smoking," and "The highest lung cancer mortality rates were found where heavy smoking was combined with exposure to air pollution." (*Brit. Med. J.* 2:1599, 1961).

Dean's estimates suggest the possibility that excessive smoking may be diagnostic of other factors predisposing to higher mortality rates; this could account for the associations found by Doll-Hill and similar studies and would also be compatible with the finding of low mortality rates for large groups of smokers in Dean, Eastcott, and the present study.

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Hammond-Horn tobacco hypothesis. Using exactly this reasoning on the cumulative 1953-1960 results, the expected frequency is 11 (four in 1953-1956 and seven in the current period), the .05 confidence interval is $11 \pm 2\sqrt{11}$ which provides a range of 4.4 to 17.6. Applying the Hammond-Horn factor of 1.7 to the expected value of 11 results in a hypothetical expectancy of 18.7 lung cancer deaths, a value that falls outside and above range of the confidence interval. Although the writers have serious reservations about the procedure suggested by Case, its application to the extended series results in a rejection of the Hammond-Horn tobacco hypothesis.

3. The additional points made by Case are hypothetical ones regarding the possible unrepresentativeness of the population and shortness of the period studied. Data with regard to some of these issues were lacking in the Haag and Hammer[2] report, but have been included above. They indicate that the representativeness of this population, and the length of time over which relevant data have now been gathered, cannot be called into serious question.

Summary

This study extends to 14¼ years mortality data of approximately 11,000 employees of cigarette factories and stemmeries in Richmond, Virginia; Durham and Reidsville, North Carolina; Louisville, Kentucky; and other locations. It confirms the findings of previous studies that this population shows lower mortality rates for all causes, for cancer, for respiratory cancer, for heart and coronary disease, than the expectancy for a population of its age, sex, and color composition based on mortality rates of the U. S. population in general. For the full period studied, the degree to which its mortality is lower than average is similar for all death causes mentioned. Independent measurement has indicated that the subject population includes more than twice as many more than 20-per-day cigarette smokers as the percentage in the general U. S. population. These findings, obtained without recourse to sampling or estimates, are contradictory to the hypothesis that cigarette smoking per se is causally related to increased mortality, from all causes, from respiratory tract cancer, or from heart disease.

The low turnover of this employee group, and the inclusion of retired and disabled personnel on the insurance rosters make this a relatively stable population suitable for an extended mortality study. The margin by which its cigarette consumption exceeds the U. S. average makes it further suited to a test of the cigarette theory.

Analysis of statistical association studies on which the cigarette theory is largely based indicates certain assumptions and criteria as to "normal" death rates which influence the final calculations of these studies. The validity of these assumptions and criteria is called into question by the results of this and other studies that do not confirm the cigarette theory.

The negative findings of these data with respect to the cigarette theory parallel and confirm the negative findings of other extended tests of the same hypothesis: that of Eastcott, who studied cancer mortality of the entire census population of New Zealand and of immigrants of similar stock from the U. K. over a 10-year period; and that of Dean, who studied lung cancer mortality among male white native South Africans and male white immigrants from the U. K. to South Africa, also over a 10-year period.

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An apparent interplay of factors relating to smoking and occupation turned up in a short-term study of the development of coronary heart disease in a general North Dakota population (Zukel et al., 1071). Farmers had about half the incidence of myocardial infarction experienced by others. In farmers, smoking had no appreciable effect on the incidence of infarction, but in others the incidence of infarction was twice as high among smokers as among the non-smokers. The farmers who smoked cigarettes smoked less heavily than males in other occupational groups.

In Chapter 5, Mortality, there is summarized the most recent information available from 7 large completed or current prospective smoking and death rate studies (Doll and Hill; Hammond and Horn; Dorn; Dunn, Linden and Breslow; Dunn, Cutil and Breslow; Best, Josie, and Walker; and Hammond). The median mortality ratio for coronary disease of current cigarette smokers to non-smokers is 1.7 (range 1.5–2.0).

Table 2 presents data from some of the large prospective studies on the ratio of mortality rates due to coronary heart disease of male smokers to non-smokers, by age and amount smoked. The ratios tend in general to increase with amount smoked and to decrease with advancing age.

The data from the first 22 months of Hammond's (41) current study help to show the size of the coronary problem. For this purpose, actual numbers of deaths may be more informative than mortality ratios. Of nearly

TABLE 2.—*Ratios of mortality rates for coronary heart disease, male smokers to non-smokers, by age and amount smoked, in selected studies*

HAMMOND AND HORN—1958 (42)

Age Group	Cigarettes smoked per day		
	Less than 10	10–19	20 and over
50–54	1.4	2.0	2.3
55–59	1.4	2.0	2.3
60–64	1.3	1.9	1.9
65–69	1.2	1.6	1.6
Total (age adjusted)	1.29	1.83	(20–39) 2.15 | (40+) 2.01

BURCHLEY, DRAKE, BRESLOW—1958 (8)*

35–41		2.0
42–54		2.0
55–61		1.8
62–74		0.9

FRAMINGHAM STUDY—1962 (43)

	(less than 20)	(20 and over)
30–62	1.5	2.2

DORN—1958 (22)

Total (age adjusted)	1.22	1.76	1.75

DOLL AND HILL—1956 (21)

Age Group	Grams of tobacco smoked per day		
	1–14 Grams	15–24 Grams	25 or more Grams
35–54	2.2	3.3	4.2
55–64	0.9	0.8	1.0
65–74	1.0	0.9	1.3
75+	1.3	1.0	1.6
Total (age adjusted)	1.1	1.1	1.4

*Persons smoking 1 pack per day or more compared with those smoking less than 1 pack per day (including non-smokers).

10,000 deaths of men aged 45–79, 46 percent were ascribed to coronary disease. 51.7 percent of the 2,630 "excess deaths" associated with cigarette smoking were caused by coronary disease. In approximate terms, nearly half of middle-aged and elderly males in the United States die of coronary disease. About half of these males smoke cigarettes. Cigarette smokers have been found in several studies to have 1.7 times as high a coronary death rate as non-smokers. If cigarettes actually caused the additional coronary deaths of smokers, they would account for many deaths of middle-aged and elderly males in this country. Like other studies (19, 21, 22, 23, 42) this one shows that the ratio of smokers' coronary death rates to those of non-smokers increases progressively with the daily cigarette consumption. In addition, at each level of consumption the ratio increases with the amount of inhalation reported by the smokers. Others (21, 23, 26, 59) have indicated that the risk of death from coronary disease in male cigarette smokers relative to that in non-smokers is greater in middle age than old age, and Hammond's current study supports this. The mortality ratio was 3.09 in the age range 40–49, and in successive decades was 2.20, 1.70, and 1.20.

Men who stop smoking have a lower death rate from coronary disease than those who continue (21, 42, 47). In the study of Hammond and Horn (42) the decrease in death appeared only after a year.

Angina pectoris is less closely related to cigarette smoking than myocardial infarction and sudden death. In the combined Albany-Framingham experience (23), angina pectoris showed no overall relationship with smoking, and the association has not been strong in other studies (71, 89).

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The statistical method used in the prospective studies have been reviewed by Brownlee (Am Stat Assoc J 60: 722-738, 1965). This article is so important that it is reproduced in its entirety.

A REVIEW OF "SMOKING AND HEALTH"*†

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Although there were earlier papers in the medical literature, e.g. Müller [1], the possibility of an association between cigarette smoking and lung cancer first became common knowledge among statisticians generally with Doll and Hill's [2] retrospective paper published in 1952. A retrospective study is one in which a group of, e.g., cancer patients is classified by their smoking habits, and a second group, the controls, known to not have cancer, but sampled from the same population as the cancer patients, is also classified by their smoking habits. The resulting 2×2 table, in which in principle the two sample sizes are fixed, can be tested for independence. The evidence for the association became more convincing with the publication in 1954 of two reports on prospective studies, one in England by Doll and Hill [3] and one in the United States by Hammond and Horn [4]. In a prospective study, a population is sampled and then each individual is classified by, e.g., his smoking habits and by his experience with respect to cancer after an interval of time sufficient to allow a reasonable number of cases of the disease to develop.

I have observed amongst some statisticians a wistfulness that statistics has not so far played a larger part in science generally. Since this association between smoking and lung cancer, interpreted by many as one of causation, is of prime importance, one might have expected it to be greeted with enthusiasm and loud admiration. On the contrary, the comments and reactions of the statistical profession have been very restrained. By and large, in fact, the silence has been deafening.

In 1955, Neyman [5] pointed out a possible fallacy in retrospective studies, but carefully asserted in a footnote that he had no direct information on the association between smoking and cancer. Incidentally, this footnote contains the curious remark:

"A referee warns me that in spite of the fictitiousness of the figures in Table I and in spite of the emphasis on the methodological character of my remarks, the 'tobacco people' may pick up the argument and use it for publicity purposes."

Also in 1955, Berkson [6] and Mainland and Herrera [7] pointed out certain types of bias which could affect prospective studies.

In 1955, Cutler [8] reviewed the literature. His overall conclusion at that time was "There is disagreement whether the evidence at hand warrants a conclusion that smoking and lung cancer are causally related." He also remarked "If lung cancer should consistently occur more frequently in smokers than in non-smokers, in various subgroups of the populations studied, the cas

* An invited review article on "Smoking and Health," Report of the Advisory Committee to the Surgeon General of the Public Health Service, U. S. Department of Health, Education, and Welfare. Public Health Service Publication No. 1103. Superintendent of Documents, Government Printing Office, Washington, D. C. 20402. xvii, 387 pp. $1.25. Paper.

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for a cause-effect relationship will be greatly strengthened. To refute effectively the hypothesis that smoking is a cause of lung cancer would then require a reasonable explanation, other than causation, for the consistently observed association between smoking and lung cancer."

In 1957, Sir Ronald Fisher [9] offered such an explanation: "that cigarette smoking and lung cancer, though not mutually causative, are both influenced by a common cause, in this case the individual genotype."

Berkson in a series of papers, e.g. [10] and [11], expressed doubt regarding the demonstration of causation. He emphasized that a higher death rate was shown for almost all diseases, and that if this is accepted as reflecting the excess deaths due to smoking then about 40 per cent of all deaths among cigarette smokers must be attributed to their smoking.

In 1959 Cornfield et al [12] concluded that "the consistency of all the epidemiologic and experimental evidence also supports the conclusion of a causal relationship (of lung cancer) with cigarette smoking, while there are serious inconsistencies in reconciling the evidence with other hypotheses which have been advanced."

Of the comments of statisticians, the above seem to be among the more important.

In 1962 the Surgeon General of the Public Health Service of the U. S. Department of Health, Education, and Welfare moved to appoint a committee to "assess available knowledge in this area [smoking vs. health] and make appropriate recommendations" (page 7). It is stated (page 8) that the function of this committee was to make "an objective assessment of the nature and magnitude of the health hazard" and "this committee would produce and submit to the Surgeon General a technical report containing evaluations and conclusions." However, "Recommendations for action were not to be a part" of the committee's responsibility.

The formation of the committee was a formidable operation. The Surgeon General met on July 24, 1962, with representatives of the American Cancer Society, the American College of Chest Physicians, the American Heart Association, the American Medical Association, The Tobacco Institute, Inc., the Food and Drug Administration, the National Tuberculosis Association, the Federal Trade Commission, and the President's Office of Science and Technology. It is noteworthy that no statistical society was represented. Also the list of organisations appears to be heavily weighted towards government agencies and organisations large, general, and active in public relations, and to have low representation of societies with specifically scientific outlooks. The participants of the July 24 meeting compiled a list of 150 scientists and physicians. This list was then screened by these participants, each organisation represented having a power of veto. From the intersection of all the sets of non-vetoes (which might, but apparently did not, have turned out to be the empty set, though we are not told its size) ten were selected for the Committee. Of the ten, only one is listed as a statistician. Since a substantial fraction of the relevant issues are statistical, one might question whether a one in ten representation for statistics was sufficient. However, one further member of the Committee is listed as an epidemiologist.

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The committee met for nine sessions of from two to four days between November 1962 and December 1963, and in addition there were "uncounted" meetings of subcommittees. The committee had the assistance of a professional staff of eight, with a secretarial and technical staff of fifteen. The committee lists 189 individuals or organisations who made "contributions." The literature surveyed was enormous. A basic bibliography of more than 6000 articles from 1200 journals up to 1959 was supplemented by an additional 1100 titles provided by the National Library of Medicine. The Report lists in the references to its various chapters about 900 references. Some of the individual studies considered were themselves enormous. For Hammond's latest report [13], 68,116 volunteers enrolled 1,078,894 men and women.

The Report represents a tremendous sifting, by a large group, of an enormous literature into 387 pages, and this review will confine itself to a brief summary of its contents and an assessment of its major conclusions, with emphasis on statistical and methodological aspects.

The front matter contains no trace of a statement of date of publication. The very last page (page 387) does have as a footnote the notation "U. S. Government Printing Office: 1964 0-714-422" in which I presume the "1964" is the year of publication.

Chapter 1 reviews the evolution of interest in the possible deleterious effects of smoking and the procedures for the establishment of the Committee. Chapter 2 describes the operation of the Committee through its subcommittees, consultants, etc. Chapter 3, "Criteria for Judgment," discusses "the Epidemiologic Method." It remarks (pages 20–21) "Statistical methods cannot establish proof of a causal relationship in an association. The causal significance of an association is a matter of judgment . . . To judge or evaluate the causal significance of the association between the attribute or agent and the disease, or effect upon health, a number of criteria must be utilized, no one of which is an all-sufficient basis for judgment. These criteria include:

(a) The consistency of the association
(b) The strength of the association
(c) The specificity of the association
(d) The temporal relationship of the association
(e) The coherence of the association"

The Report does not define these terms at this point, though they are discussed in pages 182–189 in connection with lung cancer. The Report does not state whether these are jointly sufficient. Nor does this discussion of "the epidemiologic method" give any mention of the factor of self-selection, as discussed by Yerushalmy [14], Yerushalmy and Palmer [15]. Later in the Report (pages 180–181), there is a mention of selection bias, both by the operator of the survey and by the individual whose cooperation is being sought. The subsequent discussion (page 181, last paragraph) is concerned with the results of selection of the type caused by exclusion, or decreased probability of inclusion of persons sick or about to be sick: the discussion does not bear on the well-known fact that volunteers (or equivalently, cooperative persons) may, and often do, differ in their disease experience.

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Chapter 3 also has a section on "Causality," (pages 20–21), the essential part of which appears to be "It is recognized that often the coexistence of several factors is required for the occurrence of a disease, and that one of the factors may play a determinant role, i.e. without it the other factors . . . are impotent . . .

The word *cause* is the one in general usage . . . and is capable of conveying the notion of a significant, effectual, relationship between an agent and an associated disorder or disease in the host."

Presumably in the lung cancer situation *cause* must be defined probabilistically. A very over-simplified sketch might be as follows. Suppose that each individual and his circumstances and environment can be classified dichotomously on each of n classifications, so that he is either an E_1 or an E_1^c, an E_2 or an E_2^c, etc., where E_1^c is the complement of E_1, etc. Suppose now that

$$\Pr\{E_1 | E_2 E_j \cdots E_k\} \neq \Pr\{E_1 | E_2^c E_j \cdots E_k\},$$

where $E_j \cdots E_k$ is some specified subset of conditions $E_3, \cdots, E_n$. Then, for that set of conditions $E_j \cdots E_k$, the probability of E_1 given E_2 is different from the probability of E_1 given E_2^c. Since the presence or absence of E_2 affects the probability of E_1, it seems reasonable to say that E_2 is a *cause* of E_1. The practical significance of E_2 as a cause of E_1 will depend on two conditions:

(a) If the left hand side of the above inequality, though not exactly equal to the right hand side, is numerically quite close, then for that set of $E_j \cdots E_k$ the causative association may be of small practical importance.

(b) If the inequality holds only for, say, one particular subset $E_j, \cdots, E_k$, and for all other subsets equality holds, and if the subset $E_j, \cdots, E_k$ occurs in the population with low probability, then $\Pr\{E_1 | E_2\}$, while not strictly equal to $\Pr\{E_1 | E_2^c\}$, will be numerically close to it, and then E_2 as a cause of E_1 may be of small practical importance. These considerations are related to the Committee's responsibility for assessment of the *magnitude* of the health hazard (page 8). Further complexities arise when we distinguish between cases in which one of the required secondary conditions $E_j, \cdots, E_k$ is, on the one hand, presumably controllable by the individual, e.g. the eating of parsnips, or uncontrollable, e.g. the presence of some genetic property. In the latter case, it further makes a difference whether the genetic property is identifiable or non-identifiable: for example, it could be brown eyes which is the significant subsidiary condition E_j, and we could tell everybody with not-brown eyes it was safe for *them* to smoke.

Chapter 4 is a set of Summaries and Conclusions. Chapter 5 gives consumption of tobacco products, including chewing tobacco and snuff, for the United States for selected years from 1900 to 1962. Chapter 6 is on "Chemical and Physical Characteristics of Tobacco and Tobacco Smoke." Chapter 7, "Pharmacology and Toxicology of Nicotine," concludes that nicotine is unlikely to be important.

In Chapter 8 we come to a discussion of the relationship between smoking and mortality. Subsequent chapters deal with specific groups of diseases: 9, Cancer; 10, Non-Neoplastic Respiratory Diseases; 11, Cardiovascular Diseases; 12, Other Conditions. Chapter 13, "Characterization of the Tobacco

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Habit," concludes that smoking is a *habituation* rather than an *addiction*, "since once established there is little tendency to increase the dose," etc. (page 354). Chapter 14, "Psycho-Social Aspects of Smoking," states that "The overwhelming evidence points to the conclusion that smoking is to a large extent psychologically and socially determined" (page 377). The "psychologically" part of this conclusion is apparently based on Eysenck [16] who found that cigarette smoking was positively associated with extroversion, and that both non-smokers and pipe smokers (the study was made in England, so presumably there were too few cigar smokers to consider) were less extroverted.

The evidence for the "socially" part of the conclusion seems in its summarized form to be not very quantitative. The Report forms the conclusion that "white collar professional, managerial and technical occupations contain fewer smokers than craftsmen, salespersons, and laborers" (page 363), but does not give any figures. However, "As to separate class-linked variables, income does not seem to be related in a consistent manner to prevalence of smoking." The Report finds "The relationship between smoking and education is unclear," and "The proportion of smokers is roughly the same among whites and non-whites." Men smoke more than women, though the discrepancy has been decreasing in recent years. Also, "Smoking (of any kind) is most prevalent among the divorced and widowed and least among those who have never been married, except that among persons over 45, never married are as likely to be smokers as the married" (page 364). Some religions affect smoking, and the rural farm population smoke less than the rural non-farm population. There is little difference between the latter and the urban population. Few figures are quoted in this discussion, so one cannot assess how important these various factors are.

Chapter 15 deals with the morphological constitution of smokers. What seems the most useful information is from Seltzer [17], who in 1942 obtained anthropometric measurements on 922 Harvard undergraduates and in 1950 ascertained their smoking habits (with an 81 per cent response). He found that cigarette only smokers were statistically larger in a number of anthropometric indices than non-smokers, averaging 4.37 pounds heavier, pipe only smokers larger still, and cigar smokers the largest. The Report concludes, however, "The available evidence suggests the existence of some morphological differences between smokers and non-smokers, but is too meagre to permit a conclusion" (page 387). The Report does not give reasons for declining to accept Seltzer's results.

We turn now to a detailed consideration of Chapters 8 and 9.

Chapter 8 reviews the seven major prospective studies and concludes that the overall death rate for cigarette smokers is about 70 per cent higher than for non-smokers. For cigar and pipe smokers the effect was minor. The mortality ratio, i.e. the ratio of the death rate for cigarette smokers to the death rate for non-smokers, was particularly high for certain diseases, e.g. cancer of the lung (10.8), bronchitis and emphysema (6.1), etc. For coronary artery disease the mortality ratio was 1.7. It seems that for effectively all causes of death (even accidents, suicide, and violence) the cigarette smokers had the higher death rate. Though cancer of the lung had the highest mortality ratio "coronary artery disease is the chief contributor to the excess number of deaths

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of cigarette smokers over non-smokers" (page 113). This chapter makes no explicit claim that cigarette smoking is the cause of the mortality ratios being greater than 1.

Chapter 8 reaches its conclusions solely on the basis of seven prospective studies, presumably (though nothing is stated) for the reason that its authors were aware of the hazards in attempting to make rigorous inferences from retrospective studies (possible biases in retrospective studies are discussed in Chapter 9, pages 180–181). The main difficulty, it seems to me, is that it is very difficult to define accurately the population from which the hospital sample of, e.g., cancer patients has been drawn, and even more difficult to draw a sample of controls from that population.

In some of the prospective studies a clearly defined population existed, e.g., policy holders of U. S. Government Life Insurance Policies, and the intention was to take a 100 per cent sample of this population, but in general for these studies non-response averaged 32 per cent. Biases in the non-respondents could play havoc with inferences based on the respondents. Appendix I to Chapter 8 considers this, and on various assumptions about the behavior of the non-respondents concludes that such biases could, under rather extreme assumptions, make an actual mortality ratio of, for example, 4.0 be observed as 5.0, or an actual 7.0 be observed as 10.0. The possible effects of the non-respondents are tricky, however, as Doll found (page 97) that for British doctors the non-respondents had a higher death rate and relatively more smokers than the respondents. The cross-classification is, however, not given.

In other prospective studies, e.g. the 1963 Hammond study, there is no clearly defined population and hence the concept of percentage response is impossible to evaluate. Bias could exist in the recruitment into the sample, but it is stated (page 181) that its effects, if any, should decrease with time, and this is not observed. Mainland and Herrera [7] had previously wondered about the effects of biases in studies of this type, but the Report cites the gradual increase in the mortality ratio with time as weakening their criticism. The 1963 Hammond study specifically excluded "persons too ill to answer a questionnaire" (also illiterates, and persons who could not have been traced). Presumably these exclusions are responsible for the age adjusted death rate of the Hammond sample being substantially below that of U. S. males generally. In fact, for all seven prospective studies the samples are healthier than U. S. males (page 95). This may be largely due to the probable fact that the surveys are drawn from relatively high socio-economic groups. In specific surveys other reasons may also operate.

Even though cancer contributes only 26 per cent to the total excess number of deaths of cigarette smokers, it receives the most attention in the Report, as Chapter 9 being 136 pages is substantially the largest. Lung cancer, which contributes 16 per cent to the total number of excess deaths, receives the greatest emphasis and we will confine our attention accordingly.

Chapter 9 first reviews age-adjusted mortality rates for various countries, for various times (1900–1960), by site, by sex, income class, occupation, and ethnic group. It then discusses various carcinogens, some of which are present in tobacco smoke. Then follows pages 149–196 on lung cancer, reaching the

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conclusion (page 199) "Cigarette smoking is causally related to lung cancer in men." We will now summarize the arguments that led to that conclusion.

Pages 150–161 review 29 retrospective studies and, briefly, the 7 prospective studies that had been discussed in Chapter 8. There follows a discussion of attempts to induce lung cancer with tobacco extracts and tobacco smoke in experimental animals. These have not been successful. However, industrial carcinogens were effective. Another section (page 167) reports that "genetic factors exert a determining influence on the spontaneous development and induction of lung tumors in mice."

Pages 175–176 discuss the correlation of national crude male death rates for lung cancer with per capita consumption of cigarettes. Using a 20 year lag, Doll obtained $r = 0.73$ with 11 countries. The "population" from which these 11 countries were "sampled" is not described.

Pages 179–182 discuss possible biases being responsible for the observed association, and concludes that the observed association is real.

The Report then moves to establish the causal significance of the association, its arguments following the five criteria that Chapter 3 listed as being part (or all?) of the "epidemiologic method."

(a) The first criterion is "consistency." The 29 retrospective and the 7 prospective studies all demonstrate the same association.

(b) "The most direct measure of the strength of the association between smoking and lung cancer is the ratio of lung cancer rates for smokers to non-smokers . . . " It is high, of the order of 9 to 1. Also "Important to the strength as well as to the coherence of the association is the dose-effect phenomenon. In every prospective study that provided this information, the dose-effect was apparent . . . "

(c) The specificity of the association "implies the precision with which one component of an associated pair can be utilized to predict the occurrence of the other." This seems a curious use of the word "specificity." A more satisfactory definition would seem to be Yerushalmy and Palmer's [15] "The basic assumption of such a test for specificity is that if the characteristic is not related to the disease in a causal way, then the relationship should not be restricted to the disease under study but should also be present with other disease entities. If the characteristic can be shown to be related only or mostly to the disease under study and not to many other disease entities, then our confidence that it is a cause-carrying vector for that disease is greatly increased."

This section of the Report discusses both these interpretations, its own and Yerushalmy and Palmer's, of "specificity." On the first, it comments that with diseases with multiple causes one cannot expect high specificity in this sense.

On the second, the Report states "The number of diseases in which the ratios remain significantly high, after consideration of the non-response bias, is not great enough to cast serious doubt on the causal hypothesis."

It further comments that even a single substance might cause several diseases and a mixture of substances, such as occur in tobacco smoke, might "produce more than a single disease." The Report concludes "Thus, it is reasonable to conclude that the association between cigarette smoking and lung cancer has a high degree of specificity."

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(d) The next section, "Temporal Relationship of Associated Variables," makes the point that people smoke and then have cancer, rather than vice versa. The point of course, is that if *B* occurs later in time than *A* then it is difficult to maintain that *B* is a cause of *A*. This is obviously a necessary condition, but not sufficient.

(e) The final criterion is the "Coherence of the Association" which covers a number of points as follows.

(1) The historical increase in cigarette consumption is correlated with the historical increase in lung cancer.

(2) The sex difference in smoking is in the same direction as the difference in lung cancer rates.

(3) Page 186 reports that "although adjustment for smoking history does not equalize the urban-rural lung cancer mortality ratio, control on the urban-rural residence factor nevertheless leaves a large mortality risk difference between smokers and non-smokers." This seems to imply that correlation of residence with smoking cannot account for the observed association of lung cancer rate with smoking, and, vice versa, correlation of smoking with residence cannot account for the observed association of lung cancer with residence.

(4) A section on socio-economic differentials in lung cancer mortality remarks (page 187) "it will be nevertheless noted that the professional and farmer and farm manager groups had higher proportions of non-smokers among them than did the laborers and craftsmen. This finding is in the proper direction for compatability with the socio-economic differential in lung cancer mortality but the disparity does not appear to be sufficient to provide a satisfying correction."

(5) This section comments on the dose-response relationship and refers to the muddled position with respect to inhalation.

A section on the histopathologic evidence (page 189) refers mainly to work by Auerbach on epithelial changes in the trachea and bronchi:

"These changes were rarely seen among non-smokers, but increased in frequency and intensity with the number of cigarettes smoked daily by individuals without cancer and were most frequent and intense in patients dying of lung cancer." The opinion is expressed (page 172) "it seems probably that some of the lesions found in the tracheobronchial tree in cigarette smokers are capable of developing into lung cancer."

It is difficult for one not a specialist in this area to assess the significance of these observations. The Report concludes (page 189) "Thus, the histopathologic evidence derived from laboratory and clinical material support the cigarette smoking—lung cancer hypothesis" so the Committee does not appear to regard this time as crucial. Presumably having established to its satisfaction that smoking causes lung cancer since the criteria of the "epidemiologic method" are allegedly satisfied, the Report in pages 190–193 discusses the "Constitutional Hypothesis," i.e. "the alternative hypothesis that both smoking of cigarettes and cancer of the lung have a common cause . . ." and concludes "that genetic factors play a minor role" (page 192). The main

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reasons for this conclusion appear to be (a) the presumption that the genetic hypothesis would have to be very complicated to include the dose-response relationship, etc., and (b) the rapid historical rise of lung cancer.

Finally, sundry factors such as occupational hazards, urbanization, air pollution, etc., are mentioned, and on page 196 the conclusion of causality is unequivocally stated.

This review has so far been largely restricted to a summarization of the relevant arguments leading to the above important conclusion. I will now discuss the question of whether the available evidence justifies the Report in reaching that conclusion. It is possible, of course, for the conclusion to be in fact correct but for the evidence in its favor to be inadequate. We are all familiar with the accused who has to be found not guilty, because of insufficient evidence, though we are personally certain of his guilt. Let us now comment on various parts of the Report's position.

In my opinion a key factor in determining one's opinions is one's interpretation of Table 26, pages 109–110, which shows the mortality ratios, individually by separate study and also jointly, for 25 causes of death, ordered from cancer of lung with a total mortality ratio of 10.8, bronchitis and emphysema with a total mortality ratio of 6.1, down to cancer of the rectum (1.0) and cancer of the intestines (0.9). The latter cause of death is the only one out of the 25 to show a total mortality ratio of less than 1. The total over all studies column of Table 26 is reproduced here as Table 1. The median of the 25 total mortality ratios is 1.5, and 8 are greater than 2.0. One could adopt an extreme null hypothesis attitude and admit that only those causes of death for which the total mortality ratio was statistically significantly greater than 1 are genuinely associated with cigarette smoking. The technical details of this statistical problem would be difficult on account of the various "sampling" procedures involved, allowances for possible biases and dependencies, the varying sample sizes, and the multiplicity of the tests being made. If we take the twenty-first cause of death, "accidents, suicides, and violence," with a total mortality ratio of 1.2, it is noteworthy that in each of the seven separate studies the mortality ratio is greater than 1. In my opinion virtually every tabulated cause of death shows a mortality ratio greater than 1. I do not regard even the twenty-fifth cause of death, cancer of the intestines, as significantly an exception to this, as if we look at estimates of 25 parameters the smallest of the 25 is likely to be smaller than its population value, and at 0.9 it would not take much of a sampling error to bring the ratio over 1. However, whether one feels that probably all 25 causes of death have mortality ratios greater than 1, or merely the first 21 out of the 25, or the first 15, makes little difference in my opinion. In the discussion I give below, I shall use the phrase "virtually all causes of death" but it could be replaced by some such phrase as "21 out of 25 causes of death" without changing appreciably the import of the discussion.

One's interpretation of Table 26 determines whether one accepts the Report's conclusion (page 185) "Thus, it is reasonable to conclude that the association between cigarette smoking and lung cancer has a high degree of specificity" as, on the one hand, reasonable, or on the other hand, as an extraordinary statement completely in violation with the facts. The Report

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TABLE I. NUMBERS OF EXPECTED AND OBSERVED DEATH FOR SMOKERS OF CIGARETTES ONLY, AND MORTALITY RATIOS, TOTALLED OVER ALL SEVEN PROSPECTIVE STUDIES. TAKEN FROM TABLE 26, PAGE 110, OF THE REPORT

Cause of death	Deaths		Mortality ratio
	Expected	Observed	
Cancer of lung	170.3	1,833	10.8
Bronchitis, emphysema	89.5	546	6.1
Cancer of larynx	14.0	75	5.4
Cancer of oral cavity	37.0	152	4.1
Cancer of esophagus	33.7	113	3.4
Stomach and duodenal ulcers	105.1	294	2.8
Other circulatory diseases	254.0	649	2.6
Cirrhosis of liver	169.2	379	2.2
Cancer of bladder	111.6	216	1.9
Coronary artery disease	6,430.7	11,177	1.7
Other heart diseases	526.0	868	1.7
Hypertensive heart disease	409.2	631	1.5
General arteriosclerosis	210.7	310	1.5
Cancer of kidney	79.0	120	1.5
All other cancer	1,061.4	1,524	1.4
Cancer of stomach	285.2	413	1.4
Influenza, pneumonia	303.2	415	1.4
All other causes	1,508.7	1,946	1.3
Cerebral vascular lesions	1,461.8	1,844	1.3
Cancer of prostate	253.0	318	1.3
Accidents, suicides, violence	1,063.2	1,310	1.2
Nephritis	156.4	173	1.1
Rheumatic heart disease	290.6	309	1.1
Cancer of rectum	207.8	213	1.0
Cancer of intestines	422.6	395	.9
All causes	15,653.9	26,223	1.68

accepts "specificity" as one of the criteria of "the epidemiologic method" (pages 20, 183), and in my opinion the way it claims the facts are in conformity with the criterion is to flatly ignore the facts.

In my opinion, therefore, Table 26 raises difficulties which the Report totally fails to face up to. The difficulties are as follows.

If one believes that the observed association between smoking and lung cancer is substantially real, and not an artefact of biased sampling, then one would seem required also to accept the observed association between smoking and almost all causes of death as substantially real.

If one believes that the observed association between cigarette smoking and virtually all causes of death is substantially real, then one must take one of the following positions:

(a) All the associations are due to causation.
(b) Some of the associations are due to causation and others to correlations, concealed or otherwise.
(c) All of the associations are due to correlations, concealed or otherwise.

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Positions (a) and (c) may present the fewest difficulties. If one adopts position (a), then one is under some obligation to provide hypotheses as to possible mechanisms, or to hold out hope that future research will provide these hypotheses. The difficulty with the smoking hypothesis is that it has not really got to first base on even lung cancer, let alone the other 24 causes of death, even though the matter has been under intensive investigation for ten years or more.

The most potent carcinogen identified in tobacco smoke is benz (a) pyrene (page 27) and "it is present in much larger quantity than any of the other carcinogens listed." Cigar smoke has almost 4 times as much benz (a) pyreme, and pipe smoke about 10 times as much as cigarette smoke (page 58), yet pipes and cigars are pretty well innocent of the charge of association with lung cancer. (However, the Committee does conclude that the smoking of pipes is causally related to cancer of the lip (page 204).)

Apart from the above specific measurements on smoke, the difference between cigarettes and cigars (and pipes) is a puzzling feature of the indictment of tobacco. It could be, of course, that the variety of tobacco used differs significantly, that the tobaccos are cured differently, that cigars and pipes do not use cigarette paper, that possibly pipes and cigars burn at lower temperatures, or that many cigarette smokers inhale whereas few pipe or cigar smokers do. But if inhalation is the crucial item, then it should show up strongly when cigarette smokers are analyzed into inhalers and non-inhalers, and as reported above, the present evidence on this point is not clear.

As stated earlier, animal experiments to demonstrate carcinogenic effects of tobacco smoke have proved unsuccessful.

While hypotheses for a causative effect for lung cancer are still unsatisfactory after a decade of research, the situation is even emptier for other diseases.

The degree of one's belief in the plausibility of the smoking hypothesis thus is considerably affected by the extent to which one thinks it probably that satisfactory mechanisms will be provided to account for all, or most, of the diseases.

If one adopts position (b), then one is in the unenviable position of admitting that concealed correlations account for diseases D_i, $i=k, k+1, \cdots, n$, but are not responsible for diseases D_i, $i=1, 2, \cdots, k-1$. It seems to me that once one admits that concealed correlations account for a substantial number of the observed associations, then one has to work very hard to disprove the hypothesis that they may account for all the observed correlations.

The Report uses the historical correlation of rise in lung cancer mortality with increase in per capita consumption of cigarettes as one factor to support the coherence of the association (page 185). All statisticians know that the presence of a positive, zero, or negative correlation between two variables observed over time has been the basis of more ludicrous nonsense than any other statistical procedure. For example, the incidence of cancer of the stomach has been declining for many years (Dorn and Cutler [18]), but only a madman would infer that the increased smoking has caused the decreased stomach cancer. Incidentally, it is surprising that the Report makes no mention of this fact in the section on stomach cancer (pages 225–229) though it is mentioned

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on page 135. The Report omits any comment on the weakness of this item in its discussion of the "Coherence of the Association" on page 185.

Similar considerations apply to spatial correlations, which are presented on page 176.

The fact that the hypothesis that cigarette smoking is a cause of cancer appears by and large to be in conformity with the data, and hence that this hypothesis is acceptable, does not rule out the possibility that there are other hypotheses also in conformity with the data. As Sir Ronald Fisher [19] wrote almost thirty years ago:

"For the logical fallacy of believing that a hypothesis has been proved to be true, merely because it is not contradicted by the available facts, has no more right to insinuate itself in statistical than in other kinds of scientific reasoning." And as Yule [20], quoted by Irwin [21], wrote about forty years ago: " 'You can prove anything by statistics' is a common gibe. Its contrary is more nearly true—you can never prove anything by statistics. The statistician is dealing with the most complex cases of multiple causation. He may show that the facts are in accordance with this hypothesis or that. But it is quite another thing to show that all other possible hypotheses are excluded, and that the facts do not admit of any other interpretation than the particular one he may have in mind."

It is not clear to me what are the optimal, or even satisfactory, procedures for inference. In the case where there are two competing hypotheses, one might estimate the "plausibility ratio," analogous to the likelihood ratio, and if it is very small, $\ll 1$, or very large, $\gg 1$, one can reach a conclusion. If the plausibility ratio is in the neighborhood of 1, then no decision can be reached. One would further wish that if the more plausible hypothesis is chosen as a null hypothesis, then a test of this null hypothesis can be accepted at a large P value, for otherwise one would suspect that neither hypothesis was correct, and if the less plausible hypothesis is tested as a null hypothesis one would want to it be rejected at a small P value.

The main alternative to the smoking causes-cancer hypothesis is the genetic hypothesis, and there are several odd pieces of information that give plausibility to it.

(1) There is some evidence that non-smokers, cigarette smokers, and pipe and cigar smokers are morphologically different (Chapter 15, reference to Seltzer [17]).

(2) There is some evidence that the various classes of smokers and non-smokers are psychologically different (Chapter 14, reference to Eysenck [16]).

(3) There is some evidence that identical twins are more alike than non-identical twins in their smoking habits (page 190, references to Fisher [22], Friberg et al [13], and Raaschou-Nielsen [24]).

(4) "Foreign-born migrants to the United States as a group have age-adjusted death rates for cancer of the esophagus and stomach about twice those recorded for native-born white males and females," etc., (page 134).

(5) "The several ethnic groups in the United States display their own characteristic patterns of successes and deficits in risk by site" of cancer (page 135).

It is true, of course, that these phenomena ((4) and (5)) could be the result

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of social, dietary, or other customs imported by the immigrants and maintained for one or more generations, or could be a confounding of the effects of the environment of the region of the U. S. in which each ethnic group tended to settle. Thus these phenomena can be interpreted in terms of environmental effects rather than genetic effects.

(6) Yerushalmy [14] presented data strongly suggesting that whether or not the husband smokes is associated with the incidence of premature births.

(7) Hammond [13] gives results showing marked association of death rate with longevity of parents and grandparents.

On my reading, the main reasons the Report gives for rejecting the genetic hypothesis are (1) the necessary complexity of the genetic hypothesis, and (2) the unlikelihood that the genetic pool can have changed sufficiently in the past fifty years to account for the historical rise in lung cancer rate.

For the first difficulty, different genotypes need to be hypothesized for the various classes such as cigarette smokers, cigarette smokers who give up cigarette smoking, cigar smokers, etc. It seems to me that an enormous number of traits are transmitted genetically, from color of skin and tendency to diabetes and tendency to baldness, and it is completely plausible that the tendency to be a cigarette smoker in varying degrees, a pipe or cigar smoker, and so on can be carried by the genetic code.

The second objection referred to above seems to me to overlook a possible fallacy in the interpretation of historical change in death rates. Firstly, possibly part of the long term apparent rise may be an illusion caused by fashions in diagnosis and by improvements in diagnostic techniques. It is quite probable that several decades ago many cases of lung cancer would have been diagnosed as tuberculosis. The Report claims (page 140) that over the shorter term, from 1947 on, particularly for data for Connecticut and New York, the increase in genuine as there have been "no significant advances in diagnostic methods" and in these regions "a high percentage of the cases reported have microscopic confirmation." This comment does not quite bear on the point at issue. The suggestion of the skeptics is not that cases of tuberculosis are now being falsely diagnosed as lung cancer but on the contrary that in the past cases of lung cancer were falsely diagnosed as tuberculosis.

The second argument is more complex. The generation born in 1880 reached the age of 20 in 1900, and a substantial fraction, 24 per cent, had died by this time, presumably largely due to the traditional infectious diseases of childhood. The generation born in 1900 reached the age of 20 in 1920, and a lesser fraction of this generation had died by that age, namely 15 per cent. Therefore, the 1900 cohort at the age of 50 represents quite a different stratum from the 1880 cohort at the same age of 50, since the former includes the "weaklings" who were eliminated from the latter. The relatively large number of cases of lung cancer observed in the 1900 cohort can merely be largely those who would not have survived to run the risk of lung cancer if they had been born 20 years earlier. On this model the alleged historical increase in rate of lung cancer can be readily accounted for. The model is speculative, however.

Rather strangely, the Report does not include in the section devoted to refuting the constitutional hypothesis (pages 190–193) the observations by Corn-

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TABLE 2

	X		X^c		Sums over X and X^c	
	S	S^c	S	S^c	S	S^c
C	0.00450	0.00050	0.00005	0.00045	0.00455	0.00095
C^c	0.44550	0.04950	0.04995	0.44955	0.49545	0.49905
Sums	0.45000	0.05000	0.05000	0.45000		

field et al [12] that if the mortality ratio for smokers to non-smokers for a particular disease is k, then factor X must be present at least k times more frequently among smokers than among non-smokers. The Report does refer to this result, without citation of source, in the section on specificity (page 184), where its relevance escapes me. It is clear, however, that Cornfield et al regard this result as one of the key arguments against the constitutional hypothesis, as they cite it prominently in the Summary to their paper [12]:

"The magnitude of the excess lung cancer risk among cigarette smokers is so great that the results can not be interpreted as arising from an indirect association of cigarette smoking with some other agent or characteristic, since this hypothetical agent would have to be at least as strongly associated with lung cancer as cigarette use; no such agent has been found or suggested."

A simple arithmetical illustration of this (mathematical) phenomenon is developed below. Suppose that the population is divided 50:50 into X and X^c. Suppose that amongst X people the probability of being a smoker is 0.9 and the probability of getting cancer is 0.01, and that these probabilities are independent. Suppose further that among X^c people the probability of being a smoker is 0.1 and the probability of getting cancer is 0.001, and that these probabilities are independent. Then the resulting probabilities are in Table 2. The cancer rate among smokers is $0.00455/(0.00455+0.49545)=0.0091$ and the cancer rate among non-smokers is $0.00095/(0.00095+0.49905)=0.0019$: the mortality ratio for cancer for smokers/non-smokers is thus $0.0091/0.0019=4.79$. The X rate among smokers is $0.45/(0.45+0.05)=0.90$ and among non-smokers is $0.05/(0.05+0.45)=0.10$; the ratio for X for smokers/non-smokers is thus $0.90/0.10=9.0$. This illustrates Cornfield et al's point that the X ratio for smokers/non-smokers must be greater than the mortality ratio for smokers/non-smokers. I do not feel that the numerical values of the parameters inserted in this simple model are ridiculous, yet with independence of S and C for X and for X^c we came out with a large mortality ratio for the population as a whole. I do not see why the fact that the X ratio is larger than the mortality ratio is any embarrassment to the constitutional hypothesis.

The Report quotes various results from Hammond's latest report [13] which illustrates various phenomena which can be attributed to various constitutional hypotheses, though one could also easily construct other causal hypotheses in each case. The "effect" of the use of tranquilizers, for example is shown in Table 3. (All numbers quoted in Tables 3–6 are age standardized death rates from all causes for males.) Recalling that this data was collected by volunteers,

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TABLE 3

Tranquilizers	Never smoked regularly	Cigarettes 20+ a day
Do not use	755	1501
Use	1308	2286

TABLE 4

Fried Food	Never smoked regularly	Cigarettes 20+ a day
No Fried Food Eaten	1208	2573
Fried Food 3-4 times a wk.	642	1714

often in a "social" environment, it is probable that some tranquilizer users did not admit to this habit, and therefore appear in the "do not use" row, hence raising the death rate for this row. The real "effect" of tranquilizers is therefore probably even more dramatic than the table shows.

Tables 4, 5, 6 are from Hammond; the first two are not quoted in the Report. Hammond's data also show the well known, but as far as I know, never satisfactorily explained, differences in death rates between married, single, widowed, and divorced persons. It also shows a marked hereditary effect, a marked height effect, and a moderate education effect. Hammond does not give cross-classifications, other than on smoking.

It is noteworthy that in all the above two-way cross-classifications, and others in Hammond's report not quoted here, the smoking category always has

TABLE 5

Sleep	Never smoked regularly	Cigarettes 20+ a day
<5 hrs.	2029	3936
5 hrs.	1121	2655
6 hrs.	805	1601
7 hrs.	626	1426
8 hrs.	813	1562
9 hrs.	967	1729
10+hrs.	1898	2694

TABLE 6

Exercise	Never smoked regularly	Cigarettes 20+ a day
None	834	1416
Slight	579	1347
Moderate	486	1065
Heavy	474	998

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the higher death rate. The Report mentions an unpublished analysis supplied to the Committee by Ipsen and Pfaelzer, with the conclusion, "Further, the correlation of any of these variables with cigarette smoking was too weak to reduce markedly the correlation of cigarette smoking with mortality after adjustment for the other variable." It is a pity that the Report does not give any detail on this analysis, as it may be that this analysis would have carried the greatest conviction. However, this is speculation, and we can only judge the Report by what it contains and by its references to the published literature.

One can interpret the results of Tables 3–6 in various ways. The association with longevity of parents and grandparents probably has a genetic interpretation, though it is possible to interpret it environmentally: it could be that the grandparents settled in an environment or adopted habits and customs that were favorable to longevity, and which they passed on to the later generations. The association with tranquilizers could be interpreted as causal, as is the association with cigarettes, but it appears equally plausible to hypothesize that the need for tranquilizers, and/or cigarettes, is merely a reflection of an underlying facet of the human organisms involved. Likewise, the associations with fried food eating, sleep, and exercise can be interpreted either as causal or as concealed correlations.

It will be recalled that the Committee's assignment was "if possible, to reach some definitive conclusions on the relationship between smoking and health in general" (page v).

"This committee would produce and submit to the Surgeon General a technical report containing evaluations and conclusions" (page 8).

The Committee's "Judgment in Brief" was "Cigarette smoking is a health hazard of sufficient importance in the United States to warrant appropriate remedial action" (page 33).

The detailed conclusions cover pages 37–40; the most important are "Cigarette smoking is causally related to lung cancer in men."

"Male cigarette smokers have a higher death rate from coronary artery disease than non-smoking males, but it is not clear that the association has causal significance."

My opinion is that the Committee has not established the case for causality in lung cancer. My reasons for this opinion are, to recapitulate;

(a) This conclusion can only be justified by proving the genetic hypothesis to be false, and this the Committee has failed to do.

(b) Even if there was no competing hypothesis, the case for causality is at the present time significantly weakened by the gross nonspecificity of the association and by the absence of hypothetical physical-chemical mechanisms.

My opinion that the Committee has failed to offer a satisfactory proof of the hypothesis of causality does not imply that I believe that the causality hypothesis has been proved false. It implies nothing more than I believe that it is not possible to reach definitive conclusions at this time.

Although "Recommendations for actions were not to be part of the Phase I committee's responsibility" (page 8), yet as noted above the Committee did conclude that "appropriate remedial action" was warranted. I take this as an excuse to append some personal reflections.

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Passing over the question of whether any governmental action is warranted, each individual cigarette smoker has to decide whether to make the effort to give up cigarette smoking. To make this decision he would need to know (a) the change in his expectation of life assuming that lung cancer alone is causally connected with cigarette smoking, (b) the change in his expectation of life assuming that virtually all causes of death are causally connected with cagarette smoking.

The Report does not appear to provide these figures (searching in the Report for any particular topic is sometimes difficult as the Report has no index), which is rather surprising in view of the fact that an assessment of the *magnitude* of the health hazard was one of the Committee's prime responsibilities (page 8).

The individual cigarette smoker would then have to weight the above changes in expectation by his assessment of the question of whether the cigarette smoking was a cause. He would have to relate this expected change in expectation of life to the analogous probable expected changes in expectation of life caused by various other of his activities which probably cause decreases in expectation of life, such as over-eating, undersleeping, under-exercising, travelling by automobile, etc. He would also have to weigh the possibility of such adverse consequences of giving up smoking as in due course becoming appreciably overweight. He would have to assign utilities to the expected change in expectation of life and to the pleasure and satisfaction he gets from cigarette smoking.

It is unfortunate that the Report does not give a table of changes in expectation of life, for if the change at, say, age 30 was 10 years, then even if one assigned a probability of 1/5 to the cigarette smoking causality hypothesis being true, the net change of 2 years would give one pause to consider, whereas if the change at age 30 is only 2 years, then the net change of 0.4 years on an average expectation of about 40 years might not be taken too seriously by some people.

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In summary, a significant association has been established between cigarette smoking and the incidence of myocardial infarction and sudden death in males, especially in middle life, in population groups whose members appear so far to be similar except for smoking habits. The question of whether they are, in fact, similar except for smoking is, of course, basic to the problem of whether cigarette smoking actually promotes the development of coronary disease or whether it is closely associated with some other factor or factors which promote the development of coronary disease. It has been pointed out that angina pectoris, which indicates advanced coronary atherosclerosis, is less closely associated with cigarette smoking than is myocardial infarction, and that this suggests that any etiologic role of smoking in myocardial infarction should relate more to acute occlusive mechanisms, such as intravascular thrombosis or coronary spasm, than to the development of chronic arterial disease.

SMOKING AND NON-CORONARY CARDIOVASCULAR DISEASE

In surveys of large groups cigarette smoking has not been found to be associated with an increased prevalence of hypertension (3, 4, 19, 47, 49). The study of Hammond and Horn (40, 42) did not show an increased death rate from hypertension in smokers. However, Dorn (22) found that the death rate of cigarette smokers from hypertension with heart disease was 1.53 times that of non-smokers, and from hypertension without heart disease, 1.41 times that of non-smokers. Hammond's current study shows similar figures (41). Smoking has not been found to be associated with an increased mortality rate from chronic rheumatic heart disease (22, 41, 42).

Hammond and Horn (42) found a moderate increase in the mortality rate from cerebral vascular disease in cigarette smokers as compared to non-smokers (ratio 1.30). Dorn (22) reported a ratio of 1.33, and Hammond (41) a ratio of 1.43. Although non-syphilitic aortic aneurysm is a relatively infrequent cause of death, the mortality ratio for smokers to non-smokers in this diagnostic category is large in relation to the ratios in other cardiovascular disorders. In the study of Hammond and Horn (42) it was 2.72, and in Hammond's current study (41) it is 3.10.

It has been reported (100) that diabetic males who smoke have a 50% greater incidence of clinically detectable arteriosclerosis obliterans in the legs than those who do not smoke. In general, however, there is little information about the relation of smoking to peripheral arteriosclerosis. Most experienced clinicians advise patients with obliterative peripheral arterial disease to stop smoking (45).

Buerger's disease, or thromboangiitis obliterans, has been traditionally associated with smoking, and the literature contains numerous clinical reports describing the arrest of Buerger's disease when smoking is stopped and its reactivation on resumption of smoking. The existence of Buerger's disease as an entity separate from arteriosclerosis obliterans has been recently challenged (101), but well defended (61).

It is apparent that much more work will have to be done to determine what relationship may exist between non-coronary occlusive vascular disease, aneurysmal disease, and smoking.

CHARACTERISTICS OF CIGARETTE SMOKERS

If it could be shown that cigarette smokers and non-smokers had significant constitutional differences apart from any differences that might be caused by smoking itself, then a possibility would exist that some predisposition of smokers to a particular disease might also be of constitutional origin and not caused by smoking. Cigarette smokers have, in fact, been found to differ as a group from non-smokers, but the differences, such as serum cholesterol concentration and resting heart rate, could have resulted from the smoking habit itself, so far as present knowledge indicates.

The concentration of serum cholesterol has been found to be slightly higher in smokers than in non-smokers by a number of investigators (6, 13, 49, 63, 95), but others have found no relationship (1, 54). Dawber (19) found not only that serum cholesterol was higher in smokers than in non-smokers but also that it remained higher in those who stopped smoking.

Smokers tend to be leaner than non-smokers, but to gain when they stop smoking (3, 18, 49).

A few personality differences have been reported between cigarette smokers and non-smokers. Friedman's type A men (the coronary type) tended to be heavy smokers (33). Smokers are said to be more easily angered and to eat more when under stress (94). They have been reported to marry oftener, to change jobs more frequently, to be more often hospitalized, and to participate more actively in sports than non-smokers (60).

Thomas (91, 95) has reported that the parents of medical students who smoke have a significantly higher incidence of arteriosclerotic and hypertensive cardiovascular disease than parents of non-smokers. Clearly, this finding is open to more than one interpretation.

Smokers tend to have a higher heart rate than non-smokers (3, 94).

The matter of constitutional predisposition to smoking has been investigated in twins. It has been found (27, 28, 32) that the smoking habits of monozygotic twins are significantly more alike than those of dizygotic twins, even when members of a twin pair are brought up separately.

In spite of some bits of suggestive evidence the existence of basic constitutional differences between smokers and non-smokers is not presently established. The constitutional hypothesis, which links smoking and predisposition to disease, is discussed in detail in Chapter 9, Cancer.

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The two reports that did not describe a relationship between cigarette smoking and serum cholesterol levels are (1) Acheson and Jessop (in old men) and (54) Konttinen in young men. These are well executed studies and are reproduced in this report. This subject is discussed on pages 207 to 210. Subsequent to 1964, ten additional reports appeared indicating no relationship between cigarette smoking and hyperlipidemia..

TOBACCO SMOKING AND SERUM LIPIDS IN OLD MEN

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The interrelationships between coronary heart disease, serum lipids, and cigarette-smoking have been demonstrated by authors from several countries in recent years (Hammond and Horn, 1954; Gertler and White, 1954; Gofman *et al.*, 1955; Doll and Hill, 1956; Thomas, 1958; Karvonen *et al.*, 1959; Dawber *et al.*, 1959; Bronte-Stewart, 1961). Their work has, however, been chiefly concerned with men below or during middle age, whereas it seems that over the age of 65 years there is little relationship between death from coronary heart disease and a previous history of smoking (Doll and Hill, 1956) or between clinical evidence of myocardial ischaemia and raised serum cholesterol (Oliver, 1958; Acheson, 1961). It is therefore a matter of some interest whether serum lipids are related to smoking habits in men aged 65 and over.

Material and Method

The Sample.—The men were all pensioners on the list of Messrs. Arthur Guinness Son and Company Ltd (Dublin), and their names were selected in a random manner as follows: every man aged between 75 and 8[illegible] was chosen, between the ages of 70 and 74 every third name was omitted from the list, and between the ages of 65 and 69 alternate names were omitted. The method of selection produced 267 names in all, and each man was sent a postcard inviting him to attend in the company's medical department for clinical examination; the actual attendances (221) are shown by age in Table I, together with the numbers for whom estimations of serum cholesterol and an analysis of the serum proteins by paper electrophoresis were satisfactory.

TABLE I.—*The Sample*

Age in Years	Number of Men						
	Invited to Attend	Attended		With Complete Cholesterol Assessments		With Complete Serum Electrophoresis	
		No.	%	No.	%	No.	%
65–69	92	82	89	74	80	72	78
70–74	100	86	86	83	83	77	77
75–79	40	29	72	29	72	29	72
80–85	35	24	69	23	66	23	66
Total	267	221	82	209	78	201	75

Clinical Examination and Lipid Estimations.—Full details have already been published of clinical procedures (Acheson and Acheson, 1958; Acheson, 1961) and of biochemical and electrophoretic techniques (Acheson *et al.*, 1958; Acheson and Jessop, 1961); accordingly only an outline will be given here. The clinical examination, which was carried out by one of us (R. M. A.), included a history of smoking habits and a note about diet that permitted a rough appraisal of whether or not these old men fed themselves adequately. Blood was taken in a dry syringe between 9 a.m. and 11 a.m., after breakfast, and within 90 minutes the serum was separated by centrifuging. The serum cholesterol was estimated by three independent observers, one of whom used the method of Sackett (1925) and two that of Anderson and Keys (1956); and since the findings by the two methods did not differ systematically the results were averaged, when the three estimations were within 10% of the highest of the three. In the relatively few cases where they were not, assessments were repeated until the required agreement level was reached. Paper electrophoresis, with certain minor modifications, was carried out by the technique of Dangerfield and Smith (1955), using a horizontal EEL apparatus and a barbitone buffer (*p*H 8.6). Each strip was divided in two, light green S.F. ("lissamine" green) being used to stain the serum proteins and sudan black for the lipoproteins. The intensity of staining in the various bands was measured with an automatic reflectance scanner which incorporated its own integrator.

Tobacco and Dietary Indices.—For certain of the calculations tobacco and dietary indices have been used. For the tobacco index 1 oz. (28 g.) of tobacco a week and 5 cigarettes a day were taken as unity. Thus a man who smoked 20 cigarettes a day had an index value of 4, and another who smoked 10 cigarettes a day and 3 oz. (85 g.) of pipe tobacco a week had a value of 2+3=5. The dietary index simply enumerated the number of times a man ate meat, fish, or egg in a week; it ranged from 0 to 19, and, although it is obviously a very rough measure, the serum albumin was significantly higher in those with an index of 14 than in those with an index of less than 2; and men with an index of 2 or under had significantly less subcutaneous adipose tissue than the remainder of the sample (Acheson and Jessop, 1961).

Results

Relationship of Serum Cholesterol and Smoking With Age

The distribution of serum cholesterol in the sample is shown by five-year age-groups in Fig. 1 and that of β/α lipoprotein ratio in Fig. 2. There tended

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to be absolutely and relatively fewer men with a serum cholesterol in excess of 220 mg. among the older age-groups, with the result that the mean value fell slightly

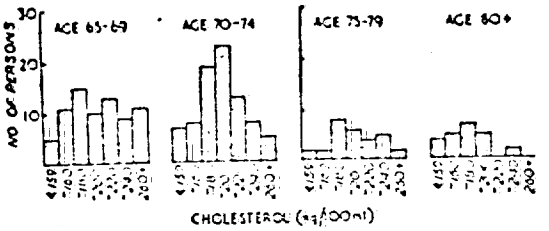

FIG. 1.—Histograms showing distribution of serum cholesterol in sample by five-year age-groups.

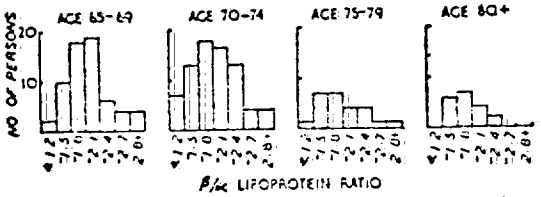

FIG. 2.—Distribution of β/α lipoprotein ratio by five-year age-groups.

but significantly with age ($r = -0.19$; $P<0.01$). The pattern of smoking varied in a far more striking manner with age (see Table II); 66% of the men aged 75 years and over were pipe smokers and 9% cigarette smokers, as compared with 27% pipe smokers and 53% cigarette smokers in those who were less than 75.

TABLE II.—*Smoking Habits by Age Among Men with Cholesterol Assessments*

Type of Tobacco Used	Age in Years			
	Under 75		75 and Over	
	No.	%	No.	%
None ..	26	17	12	23
Cigarette only ..	83	53	5	9
< 20/day ..	45	29	2	4
> 20/day ..	38	24	3	5
Pipe only	42	27	35	66
Cigarette and pipe	5	3	1	2
Total ..	156	100	53	100

Relationship Between Serum Lipids and Smoking

The nature of the relationship between smoking and both serum cholesterol and β/α lipoprotein ratio is indicated in Table III. This shows that both measures of serum lipid are just a little higher in non-smokers or very light smokers than in the heavier smokers of cigarette or pipe tobacco. This trend is confirmed by the correlation analysis shown in Table IV, where it

TABLE III.—*Relationship of Cigarette and Pipe Smoking with Serum Cholesterol and β/α Lipoprotein Ratio*

Type of Tobacco Used	Mean Serum Cholesterol (mg.)		Mean β/α Lipoprotein Ratio	
	No.	Mean	No.	Mean
None ..	38	214	36	2·0
Cigarette only; No./day:				
5	12	201	11	2·1
10	34	213	33	1·9
20	33	201	33	1·9
30 and over	8	206	8	1·8
Pipe only; oz./week:				
1	3	203	3	2·2
2	25	197	23	1·7
3	21	213	19	1·9
4	17	211	17	1·8
5 and over	11	219	11	1·7

can be seen that all the coefficients of correlation are negative, but with the exception of β/α lipoprotein ratio in pipe smokers and non-smokers the trends are not statistically significant.

TABLE IV.—*Correlation Between Serum Lipids and Smoking in the Entire Sample*

	Serum Cholesterol (mg. 100 ml.)	Serum Lipoproteins β/α Ratio
Cigarette smokers and non-smokers ..	−0·07	−0·10
Pipe smokers and non-smokers ..	−0·14	−0·33*
Tobacco index	−0·01	−0·11

* $P<0.001$; none of the other statistics are significant at the 5% level.

Bronte-Stewart (1961) believes that the proved relationship between serum cholesterol and cigarette-smoking in younger men may be due to dietary preferences. It is possible that these old people living on pensions cannot afford to smoke heavily and to eat well, and therefore a comparison was made between the dietary indices and some other characteristics of, on the one hand, the heavy smokers of both cigarettes and pipe tobacco and, on the other, the non-smokers (Table V). It can be seen that the heavy cigarette-smokers are significantly younger than the other two groups—a finding which reflects the difference between the smoking habits of the generation which reached maturity before and after 1914. In the sample as a

TABLE V.—*Serum Lipids, Age, and Dietary Index of Non-smokers and Heavy Smokers of Cigarette and Pipe Tobacco*

	No.	Age in Years		Cholesterol (mg.)		β/α Lipoprotein Ratio		Dietary Index	
		Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
Non-smokers	38	72·4	5·1	214·5	42·9	2·0	0·4	7·1	3·6
30 cigs. day or more	8	67·7*	1·9	205·7	37·3	1·8	0·3	7·0	2·3
5 oz. pipe tobacco/week or more ..	11	72·3	4·1	216·8	65·0	1·7	0·3	9·4	4·9

* Significantly younger than the other two groups ($P<0.02$); no other group differences are significant at the 5% level.

whole there was a significant negative regression of serum cholesterol with age of 1.7 mg./year (Acheson *et al.*, 1958), but, even allowing for this, the differences between the mean serum cholesterol values are not significant at the 5% level. The dietary index used in this study does not measure preferences, but it has already been shown above that there is reason to believe that it measures the general level of nutrition and therefore would show whether the heavy smokers go without food. The analysis in Table V indicates that this is not the case; indeed the heavy pipe-smokers eat rather more than the non-smokers, although the difference is not quite significant ($t=1.69$; $0.1>P>0.05$).

Discussion

There can be little question of the relationship between serum lipids and cigarette-smoking in middle-aged men. It has been demonstrated in the U.S.A. (Gofman *et al.*, 1955; Thomas, 1958; Dawber *et al.*, 1959), Finland (Karvonen *et al.*, 1959), and South Africa (Bronte-Stewart, 1961); yet in the present data based on old men there is no evidence whatsoever of such a relationship—in fact, there is a suggestion that non-smokers may have a mean serum cholesterol and β/α lipoprotein ratio which are higher than in smokers.

Bronte-Stewart (1961) believes that the reason serum lipids are raised in younger smokers is because taste preferences induce them to eat more cholesterologenic

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substances, such as saturated fats, than non-smokers; he has published some evidence, which he does not claim to be conclusive, to support his view (Bronte-Stewart, 1961; Perrin *et al.*, 1961).

The lack of correlation between serum lipids and smoking habits in the present sample receives indirect support from the fact that smoking does not seem to be associated with coronary heart disease in them (Acheson, 1961) or in two other samples of men over the age of 65 years (Hammond and Horn, 1954; Doll and Hill, 1956). On the present evidence it is not possible to give a reason for this, even less to explain the possibility of an inverse relationship, but several theories suggest themselves. First, as has been stated, limited financial means might have caused those who smoke more to eat less, but in the present sample there was nothing to suggest that means were so limited nor that heavy smokers ate less. Secondly, if we accept Bronte-Stewart's basic hypothesis, it could reasonably be argued that the effect of ageing on the sense of taste may be more powerful than any effect of tobacco-smoking, so that the latter is obscured among old people. Thirdly, it could be that with increasing age the pattern of metabolism of fats and lipids is changed.

Our finding, although difficult to explain, is compatible with our knowledge of the aetiology of coronary heart disease in old men. In younger age-groups the greater part of coronary disease takes the form of infarction caused by thrombotic occlusion of a major vessel, a lesion which has repeatedly been shown to be associated with high serum cholesterol and a raised β/α lipoprotein ratio. Bronte-Stewart (1961) believes that the relationship between cigarette-smoking and such disease is due to the raised serum cholesterol which smokers have, rather than to any pharmacologically induced response smoking may elicit from the cardiovascular system. Only 9%, of the present series had myocardial *infarction*, and in them the serum cholesterol and β/α lipoprotein ratios were raised; the remaining 81%, the majority of whom had angina pectoris and/or myocardial ischaemia, did not differ from the controls in their smoking habits or their serum lipids or serum cholesterol. Dawber *et al.* (1958), in a longitudinal study of younger men, have shown that, although cigarette-smoking and high serum cholesterol predispose to coronary thrombosis, neither predisposes to new cases of coronary heart disease presenting as angina pectoris. In line with this is the failure of Paterson *et al.* (1956) to demonstrate a correlation between cholesterol levels during life and the extent of atherosclerosis at necropsy. Our present finding, therefore, is consistent with the view already expressed (Acheson, 1961) that coronary heart disease which presents as angina pectoris and electrocardiographic evidence of myocardial ischaemia without infarction in old men is of different aetiology from acute coronary thrombosis, which is the more usual form the disease takes in younger men.

Summary

It is shown in a random sample (221) of a defined population of men aged 65-85 years that tobacco-smoking, whether in pipes or cigarettes, is not associated with elevation of the serum cholesterol or the β/α lipoprotein ratio. The significance of this finding in the aetiology of coronary heart disease is discussed.

We are again pleased to acknowledge our gratitude to the directors of Messrs. Arthur Guinness Son and Co. Ltd. (Dublin), to Dr. Brian Pringle and Dr. J. F. Eustace, and to our colleagues in the Moyne Institute, Trinity College, Dublin, for making this study possible. Miss Jane Cooper helped with the computations and Dr. Richard Doll kindly read the text.

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CIGARETTE SMOKING AND SERUM LIPIDS IN YOUNG MEN

BY

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In mortality statistics cigarette-smoking habits have been observed to be correlated with coronary heart disease (Hammond and Horn, 1954; Doll and Hill, 1956; Hammond and Horn, 1958); and the serum lipid level and especially the serum cholesterol and β-lipoproteins are known to be raised in population groups with coronary heart disease. With these facts in mind, many investigators have studied the relationship between cigarette smoking and the serum lipid level (Gofman *et al.*, 1955; Karvonen *et al.*, 1959; Thomas, 1958, 1960; Dawber *et al.*, 1959; Blackburn *et al.*, 1960; Bronte-Stewart, 1961). All these studies support the view that the serum cholesterol level is higher in smokers than in non-smokers. The present communication shows that there was no correlation between smoking habits and serum lipid pattern in a group of young men in Finland.

Material and Methods

The material presented consists of a series of 314 healthy young men who started military service in Finland in 1957–60. The subjects were selected at random. Their mean age was 19.7 years (range 18–25). Blood samples were taken from the cubital vein in the morning after overnight fasting during the first three days of military service. From the specimens the serum total cholesterol (Anderson and Keys, 1956) and the serum total phospholipids (Fiske and Subbarow, 1925) were determined. Serum lipo-protein fractions were separated with the aid of paper electrophoresis, and from the fractions so separated the cholesterol content of the α- and β-lipoproteins was determined. The details and evidence of their accuracy have been presented in a previous study (Konttinen, 1959). Blood-pressure was also measured and relative body weight was calculated according to the Metropolitan Life Insurance Company's (1943) tables. To be sure that the men were healthy, determinations were also made of the blood sedimentation rate and blood haemoglobin level, and the urine was analysed for glucose and protein. Mass x-ray examinations of the chest were also made.

The smoking habits were reported in response to a questionary filled in by each man. There were 145 men who had never smoked. The smokers, divided into subgroups according to daily consumption of tobacco (see Table), had smoked for at least one year before entering military service. The few pipe smokers were not included in the series. Nearly all the smokers smoked American-type cigarettes with or without a filter.

Results

In the different groups the similarity in level of all the lipids studied (see Table) is obvious. Statistically there is no difference between the groups in total cholesterol, β-cholesterol, or phospholipids. Analysis reveals a probable difference ($P<0.05$) in α-cholesterol variance, but this seems not to depend on the smoking, since this difference is between light smokers and non-smokers. On the other hand, between non-smokers and heavy or moderate smokers there appears to be no significant difference in α-cholesterol.

Discussion

In the present study the similarity in serum lipids found in smokers to those found in non-smokers is at variance with the results of previous studies, in all of which the cholesterol level has been stated to be higher in smokers. The material presented here is very similar in all respects except smoking habits. Body build, expressed as relative body weight, was very much the same. The men came from the same parts of Finland and the occupational structure of the different groups was also similar. The blood samples had been taken similarly in the different groups in respect of time and season. The age range of the whole series is quite narrow (18–25 years) and there is very little difference between the groups. As the men were young they had not been smoking very long, although one criterion in selecting them was at least one year's smoking. Karvonen *et al.* (1959), however, observed a higher serum cholesterol level in smokers of all age-groups, except 50–59 years, in West Finland; the youngest age-group in their study was 20–29 years. Gofman *et al.* (1955) found that the difference in serum lipids between smokers and non-smokers was greater in their youngest (20–29) age-group than in the older ones. In the present study the subjects were slightly younger than the youngest age-groups mentioned above. If the explanation for the difference between the observations in the mentioned studies and the present one lies in this point, the effect on serum lipids of exposure to cigarette smoking seems to occur after some years of smoking, but not, however, during so short a smoking period as in the present work.

When considering atherosclerosis many investigators have stressed the importance of the $\beta:\alpha$ ratio in the lipoprotein fractions. It has been noticed that an increase in this ratio is encountered in patients with atherosclerosis (Nikkilä, 1953; Oliver and Boyd, 1955; Jencks *et al.*, 1956). In the studies concerning the correlation between smoking and serum lipids in which lipoprotein fractions are included the $\beta:\alpha$ ratio has been found to be raised in smokers (Gofman *et al.*, 1955; Bronte-Stewart, 1961). In the present study, by contrast, no trend parallel with the smoking habits could be discerned in serum lipid levels.

The serum phospholipids have been shown to have the important function of stabilizing other lipids in solution

Serum Lipids in 314 Young Men Grouped According to Smoking Habits

Group	No. of Cigarettes/Day	No. of Men	Serum Cholesterol (mg. %) Mean ± S.D.	Serum α-Cholesterol (mg. %) Mean ± S.D.	Serum β-Cholesterol (mg. %) Mean ± S.D.	Serum Phospholipids (mg. %) Mean ± S.D.	Relative Body Weight (kg.) Mean	Age (Years) Mean
Non-smokers		145	201.8 ± 32.5	92.8 ± 11.4	151.0 ± 34.8	210.0 ± 34.8	66.4	19.3
Light smokers	1–10	93	206.8 ± 37.0	98.2 ± 9.55	146.6 ± 34.9	222.1 ± 32.5	69.9	19.9
Moderate smokers	11–19	34	203.1 ± 34.5	95.3 ± 11.7	157.9 ± 35.5	224.7 ± 31.0	67.2	20.1
Heavy smokers	20+	42	202.3 ± 32.6	93.7 ± 10.6	144.6 ± 31.1	210.5 ± 24.6	68.2	19.8

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(Ahrens and Kunkel, 1949), and it has therefore been inferred that an increase in the ratio of phospholipids to cholesterol helps to prevent atherosclerosis. This view has been supported by the observation that the phospholipid:cholesterol ratio is smaller in atherosclerosis than in age-matched controls (Gertler *et al.*, 1950; Oliver and Boyd, 1953). The published studies on the relation between serum lipids and smoking do not include reports concerning serum phospholipids. In the present study phospholipids show no trend paralleling the smoking habits.

Attempts have been made to relate the rise in serum lipids observed in the previous studies in smokers to differences in the diet possibly due to smoking. Krut *et al.* (1961) have noted a difference in the perception of bitter taste between smokers and non-smokers. According to those authors this could lead to smokers having a preference for some special foods. The same group of investigators (Perrin *et al.*, 1961) have observed that smokers consumed more fat than non-smokers, but the difference was too small to explain the difference in serum lipids, and in Finland S. Punsar (unpublished data) could not detect any difference between the diet of smokers and that of non-smokers. Even the greater amount of fat consumed by smokers does not necessarily signify that all this fat is absorbed, for a recent study (Konttinen and Rajasalmi, to be published) has shown that the rise in serum triglycerides after a fatty meal is less in heavy smokers than in non-smokers.

The effect of giving up smoking should throw further light on the correlation between cigarette smoking and serum lipids, but in the only relevant report I found in the literature no change in serum cholesterol was detected in the six subjects studied (Thomas and Eisenberg, 1959).

The possibility has also been discussed that smoking could be another manifestation of the disturbance responsible for the rise in the serum cholesterol level, and in this connexion mental tension was incriminated as the cholesterol-elevating factor (Thomas and Murphy, 1958; Wertlake *et al.*, 1958; Grundy and Griffin, 1959; Dreyfuss and Czaczkes, 1959; Peterson *et al.*, 1960). It should be remembered, however, that mental tension cannot be measured but only estimated.

It is evident that further investigations of the relationship of smoking to the serum lipids are required.

Summary

Serum total cholesterol and the cholesterol content of the α- and β-lipoprotein fraction and serum phospholipids have been determined in a series of 314 healthy young men (range 18–25 years) starting military service, grouped according to smoking habits. There were no differences relating to smoking habits in any of the lipids studied.

Addendum.—Since the present study was made Acheson and Jessop (1961) have published their work on serum lipids in old men grouped according to smoking habits. They could find no association between cigarette or pipe smoking and serum cholesterol or β:α-lipoprotein ratio.

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PSYCHO-SOCIAL FACTORS OF SMOKING IN RELATION TO CARDIOVASCULAR DISEASE

Even less conclusive information is available on the role of psycho-social factors of smoking in relation to cardiovascular disease. Studies which have focussed on this are limited in number according to Heinzelmann (44). Even fewer, he found, are those which have specifically examined the relative weight of these variables or their interaction. Reviewing those available, he observes that the evidence is highly fragmentary and uncertain. The findings suggest that the relationship between smoking behavior and coronary heart disease may reflect the influence of stress factors and/or personality mechanisms. However, they permit no definitive statements with respect to the relative role of psycho-social factors and smoking in relation to etiology of the disease.

SUMMARY

Smoking and nicotine administration cause acute cardiovascular effects similar to those induced by stimulation of the autonomic nervous system, but these effects do not account well for the observed association between cigarette smoking and coronary disease. It is established that male cigarette smokers have a higher death rate from coronary disease than non-smoking males. The association of smoking with other cardiovascular disorders is less well established. If cigarette smoking actually caused the higher death rate from coronary disease, it would on this account be responsible for many deaths of middle-aged and elderly males in the United States. Other factors such as high blood pressure, high serum cholesterol, and excessive obesity are also known to be associated with an unusually high death rate from coronary disease. The causative role of these other factors in coronary disease, though not proven, is suspected strongly enough to be a major reason for taking countermeasures against them. It is also more prudent to assume that the established association between cigarette smoking and coronary disease has causative meaning than to suspend judgment until no uncertainty remains.

CONCLUSION

Male cigarette smokers have a higher death rate from coronary artery disease than non-smoking males, but it is not clear that the association has causal significance.

(44) Heinzelmann, F. Special report to the Surgeon General's Advisory Committee on Smoking and Health.

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The contents of the Summary and Conclusion have been widely quoted in several publications listed in pages 322 to 343. The Editorial by Hutchison (Bull N Y Acad Med 44: 1471-1475, 1968) is one of a few that has discussed the limitations of the epidemiologic approach. The article is reproduced below.

THE NATURE OF EPIDEMIOLOGIC EVIDENCE: SMOKING AND HEALTH*

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THE SURGEON GENERAL'S REPORT

In 1964 the Advisory Committee to the Surgeon General of the Public Health Service identified a number of disease categories for which the committee was willing to state that a causal association with cigarette smoking had been established.** These were all diseases of the respiratory apparatus, including cancers of the lip, larynx, bronchus, and lung, plus one nonmalignant condition, chronic bronchitis. No cardiovascular diseases were so designated.

A second group of disease categories was identified as associated with cigarette smoking, but a causal relationship was not established. In this group were included arteriosclerotic heart disease and a category referred to as noncoronary cardiovascular disease. The noncoronary category includes endocarditis, hypertensive heart disease, and certain

*Presented at the *Conference on Smoking and the Heart* held by the New York Heart Association at The Waldorf-Astoria, New York, N. Y., March 26, 1968.

**Smoking and Health: Report of the Advisory Committee to the Surgeon General of the Public Health Service, U.S. Department of Health, Education, and Welfare, Public Health Service. Washington, D.C., Govt. Print. Office, 1964.

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residue rubrics of other heart and circulatory disease. In addition to these cardiovascular categories the associated group included cancers of the oral cavity, esophagus, and bladder, and the benign conditions emphysema, gastric ulcer, and cirrhosis.

The judgment relative to coronary disease is somewhat stronger than that relative to other conditions where a causal conclusion was not possible. The committee felt that a prudent course of action with respect to coronary disease should be based on a presumption of a causal association. Countermeasures should not be postponed while further refinement of the evidence is awaited. Subsequent data add strength to these conclusions.

Cause-Effect Concept

The concept of cause that is appropriate to discussions of the relation of smoking to illness should be considered here.

I should like to distinguish two concepts which I shall call the pragmatic concept and the elaborated theory concept. Under the pragmatic concept a cause-effect relation exists when *deliberate manipulation* of a series of preliminary alternatives is followed by a *statistically predictable variation* in a second series of alternatives. The preliminary manipulation is referred to as the cause, and the outcome in the second series is referred to as the effect. In the present discussion a pragmatic cause-effect would be proved if an investigator were to manipulate the smoking habits of a group and if the predicted incidence of disease was to follow. It should be noted that this concept does not involve either a necessary or sufficient relation. To say that smoking causes coronary disease permits the possibility that coronary disease occurs in some frequency in the absence of smoking. It also permits the possibility that some smokers, or even most smokers, will not develop coronary disease. This concept says nothing about the mechanism of the causal association. Finally the concept is of direct significance for public health action, since it indicates that a certain manipulation will improve health in some measure.

Under the elaborated theory concept a cause-effect relation is established by demonstrating that the relation is a consequence of laws of basic science. The emphasis is on mechanism. The relation must generally be stated in much more refined terms than "smoking" and "coronary disease." For example, it may be concluded that nicotine stimu-

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lates or paralyzes certain ganglia with a consequent alteration in pulse rate. This alteration may be inconsequential in normal hearts but may set off a further chain of events in hearts with previously damaged coronary arteries. The ultimate conclusion will be that smoking is followed by coronary heart disease under conditions that the smoke includes nicotine, the smoke is inhaled in specified concentrations, and the heart is previously damaged in some specified way.

A portion of the disagreement in the literature and in meetings such as this arises from a misunderstanding of which of these two cause-effect concepts is under discussion. A greater disagreement, however, rests on a judgmental decision as to what evidence is necessary to accept either concept.

Epidemiologic Evidence

An extensive literature on associations between smoking and cardiovascular disease is now available. I propose to comment on some of the studies in this literature in which the unit of observation is a person and in which information is collected to characterize persons as to state of health. These are the studies which are commonly referred to as epidemiologic studies. When these studies are interpreted in terms of cause-effect relations the cause-effect concept is usually the pragmatic one.

The proof of cause-effect would be established or rejected by deliberately manipulating the smoking habits of such persons and observing the results. No such studies have been made to my knowledge. Controversy, when it occurs, rests on differences of opinion as to what constitutes proof in the absence of such a manipulative study. There are those who feel that proof is *never* established without such human experimentation. Others feel that proof can be established through observational studies, but there is little agreement as to what sorts of observations are required.

A number of schemes have been suggested for assuring such proof. Koch's postulates are an early attempt, but are applicable only when the causative event is exposure or nonexposure to living organisms. The surgeon general's committee has proposed a number of conditions which must be satisfied. These include consistency, strength, specificity, and coherence of the association. The ultimate decision, however, is said to be judgmental.

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In general the acceptability of proof depends on the degree to which observations may be said to mimic the manipulative experiment. Perhaps the best example of such a "natural experiment" is the study that demonstrated a leukemogenic effect of ionizing radiation in the survivors in Hiroshima.

Smoking and Cardiovascular Disease

There is no study of smoking effects which closely resembles this sort of natural experiment. In all available studies persons are characterized as nonsmokers, former smokers, light smokers, heavy smokers, inhalers, and as other descriptive types with respect to the smoking habit. There is no presumption that the assignment to such a category was a chance event, and indeed some investigators have made it clear that the decision to smoke is not a chance event but is to a degree predictable on the basis of characteristics present before the decision is made, on the so-called constitutional characteristics.

We have then associations between smoking and certain cardiovascular diseases that are technically and statistically satisfactory, in the sense that they would rarely occur by chance in our samples if, in fact, smoking had nothing to do with these diseases. We have also associations between certain constitutional factors and smoking, also technically satisfactory. We may think of three possible explanations. First, the constitutional factors may lead to both smoking and disease. Second, smoking may cause disease. Third, disease may cause smoking. These three explanations may all be in effect.

If the constitutional association were a very strong one, so that all or almost all smokers and nonsmokers could be identified by eye color, for example, then we could not support the cause-effect hypothesis. But in fact the constitutional association leaves much room in which to maneuver. We can find, for example, smokers and nonsmokers within both vulnerable and nonvulnerable constitutional types.

When the diseases which are accepted by the committee as causally related are studied it is found that the relative risk is very high, often of the order of 10 to 20. This in essence means that if the cause-effect explanation is correct, it accounts for a very large part of these diseases. For example, it is possible to suppose that most lung cancer may be due to smoking and would be abolished by the cessation of smoking. With the doubtful group, relative risks of the order of 1.5 to

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3 are found, and smoking, if causal, can be incriminated in only a small portion of the cases. No one can suppose that the abolition of smoking would wipe out cardiovascular disease or even a very large part of it.

This low relative risk is no argument against the cause-effect hypothesis, but it does make it difficult to give convincing proof of the hypothesis. It opens the possibility that whatever factors cause the majority of these diseases are also responsible for the association with smoking. In the case of lung cancer many of us find it hard to believe that we could have overlooked some confounding variables that are so highly correlated with both smoking and lung cancer. With cardiovascular disease there is the troublesome suspicion that some relatively low-level association really may have been overlooked.

The strongest argument derived from epidemiologic studies in favor of the causal interpretation with respect to coronary disease is the finding that the risk diminishes with time after smoking is abandoned. It should be noted that this by no means decides the debate. It may be hypothesized that the constitutional tendency to smoke also governs the length of time a consumed individual can stay away from the habit. Those who manage to stay away for periods of 5 to 10 years may be supposed to have a low level of constitutional vulnerability to smoking.

As the evidence has accumulated in recent years, the complexity of the hypotheses necessary to contradict the causal hypothesis has increased. It is in evaluating the acceptability of these complex arguments that judgment must play the final role. It is unlikely that all informed scientists will come to the same judgmental decision when studying the same body of data. This will probably dismay many lay people, but it is a phenomenon with which scientists should be familiar. It should not be a cause for despair or distrust among scientists. Finally, it should be possible, as the surgeon general's committee has done, to recognize the point when evidence is adequate to support public health action even though it is not adequate to consider an issue closed.

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The Health Consequences of SMOKING

A PUBLIC HEALTH SERVICE REVIEW : 1967

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service

PART II

Technical Reports on the Relationship of Smoking to Specific Disease Categories

CHAPTER 1

Smoking and Cardiovascular Diseases

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SMOKING AND CORONARY HEART DISEASE

Coronary Heart Disease Mortality[1]

The relative importance of the association between cigarette smoking and coronary heart disease (CHD) as compared to the association of smoking with other diseases was previously described in the introduction to chapter 11 of the Surgeon General's 1964 Report.

In the United States more persons die from coronary heart disease than from any other single cause; and this most common form of fatal cardiovascular disease accounts for a greater percentage of excess deaths among cigarette smokers than do deaths from lung cancer. In 1964, there were 1,798,000 deaths from all causes, of which almost 545,500 or 30.3 percent, were due to atherosclerotic heart disease, including coronary heart disease. Table 1 gives the 1964 death rates for *coronary heart disease* per 100,000 persons by age and sex:

TABLE 1.—*1964 death rates for coronary heart disease per 100,000 persons by age and sex*

	All ages	25-34	35-44	45-54	55-64	65-74	75-84	85+
Both Sexes	253.1	6.9	53.2	203.8	576.3	1,284.9	2,937.7	6,852.9
Males	354.2	11.0	90.9	341.3	850.8	1,942.4	3,623.0	7,400.4
Females	213.5	3.0	17.4	76.3	259.4	926.5	2,464.0	6,550.0

SOURCE: National Center for Health Statistics [97].

These data illustrate the dramatic increases in the risk of death from coronary heart disease as age advances. For males the rates among persons over the age of 45 appear to double from one decade to the next; among females the increased risk of death with advancing age is more dramatic—a threefold increase every 10 years. Of perhaps greater importance are the relatively low death rates among females, particularly below the age of 65, compared to males of comparable age. The mortality differential between the sexes becomes less as age advances; under 45 years of age the coronary death rate among men is five times as high as among women and in the 75–84 year age group it is only about 1.5 times as high.

The Surgeon General's 1964 Report determined a median mortality ratio (*99*) (pp. 103–110) for coronary heart disease of male current cigarette smokers of 1.7. Since this report, five large prospective studies of smoking and mortality have been updated on the basis of longer periods of observation on each study subject. Current findings are therefore more definitive and permit more detailed analysis of the interrelationship of cigarette smoking to other significant variables such as age, sex, and the nature of the smoking habit in terms of amount and duration of smoking. Pertinent findings are presented below from the studies of veterans in the United States (*52*) and Canada (*14*) and the extensive data reported by Hammond (*47*), Doll and Hill (*25, 26, 27*), and Borhani (*17*).

The relative excess mortality associated with cigarette smoking is generally expressed in terms of a mortality ratio. This statistic is defined as the ratio of the number of observed deaths among smokers, to the expected deaths among smokers, if the age-specific mortality rates observed among non-smokers had prevailed (*52*). The process of computing the expected number of deaths among smokers takes into account and adjusts for any differences in the age distribution of the smokers and the nonsmokers under observation. Generally smokers are defined as persons currently smoking cigarettes, and nonsmokers as those who never smoked or who never smoked regularly.

Table 2 shows the mortality ratios for coronary heart disease deaths among current cigarette smokers according to the amount smoked daily in U.S. and Canadian male veterans.

TABLE 2.—*Coronary heart disease mortality ratios, age-adjusted among current cigarette smokers by amount smoked daily*

	Cigarettes smoked daily				
	Under 10	10-20	21-39	More than 39	40+
U.S. male veterans	1.3	1.7	1.8	.....	2.0
Canadian male veterans	1.6	1.6	.....	1.8	.....

SOURCE: U.S. veterans study (52) and Canadian pensioners study (14).

In both studies (*14, 52*) the mortality ratios were similar and increased with increasing intensity of cigarette smoking. Slightly higher ratios are reported in the U.S. veterans study for current smokers of cigarettes only.

[1] All death rates throughout this chapter are per 100,000 population, unless otherwise indicated.

(97) U.S. PUBLIC HEALTH SERVICE. National Center for Health Statistics. Mortality from diseases associated with smoking: United States, 1959–61. Washington. U.S. Department of Health, Education, and Welfare. Vital and Health Statistics Series 20, No. 4, Public Health Service Publication No. 1000, October 1966. 45 pp.

(99) U.S. PUBLIC HEALTH SERVICE. Smoking and Health. Report of the Advisory Committee to the Surgeon General of the Public Health Service. [Washington.] U.S. Department of Health, Education, and Welfare, 1964. 387 pp.

(52) KAHN, H. A. The Dorn study of smoking and mortality among U.S. veterans: report on 8½ years of observation. *In:* Haenszel, W., editor. Epidemiological approaches to the study of cancer and other diseases. Bethesda, U.S. Public Health Service, National Cancer Institute Monograph No. 19, January 1966. Pp. 1–125.

(14) BEST, E. W. R. A Canadian study of smoking and health. Ottawa, Department of National Health and Welfare, 1966. 137 pp.

(47) HAMMOND, E. C. Smoking in relation to the death rates of 1 million men and women. *In:* Haenszel, W., editor. Epidemiological approaches to the study of cancer and other diseases. Bethesda, U.S. Public Health Service, National Cancer Institute Monograph No. 19, January 1966. Pp. 127–204.

(25) DOLL, R., HILL, A. B. Mortality in relation to smoking: 10 years' observations of British doctors (pt. 1). British Medical Journal (London) 1(5395): 1399–1410, May 30, 1964.

(26) DOLL, R., HILL, A. B. Mortality in relation to smoking: 10 years' observations of British doctors (Concluded). British Medical Journal (London) 1(5396): 1460–1467, June 6, 1964.

(27) DOLL, R., HILL, A. B. Mortality of British doctors in relation to smoking: Observations on coronary thrombosis. *In:* Haenszel, W., Editor, Epidemiological Approaches to the Study of Cancer and Other Chronic Diseases. Bethesda, U.S. Public Health Service, National Cancer Institute Monograph No. 19, January 1966. Pp. 205–268.

(17) BORHANI, N. O., HIGHTOWER, H. H., BARTELOW, B. Report of a 10-year follow-up study of the San Francisco long-shoremen. Mortality from coronary heart disease and from all causes. Journal of Chronic Diseases (St. Louis) 16: 1251–1266, 1963.

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The statistical methods which appeared in the 1964 report, reappear in the 1967 one. A second article criticizing the methods is appended (from the Bulletin of National Statistical Institute, pp 856-860, 1966).

A CRITIQUE ON THE REPORT OF THE SURGEON GENERAL'S ADVISORY COMMITTEE ON SMOKING AND HEALTH

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ABSTRACT

The Report of the Surgeon General's Advisory Committee on Smoking and Health was first issued in January 1964 by the United States Public Health Service.

The critique submitted for presentation by the author is only part of a much longer version. In other words, the Report of the Surgeon General's Committee lends itself to a considerable amount of discussion.

Are the conclusions of the Surgeon General's Committee justified? The author feels that they are not and he bases that opinion on an examination of the methods employed by the Committee in arriving at its conclusions, the character of the Report itself and the composition of the Committee as far as scientific disciplines are concerned. In that respect, his critique can be summarized as follows:

1. In its Report, the Surgeon General's Committee did not make a clear distinction between *causal significance* and *proof* and, on one occasion, did use the terms interchangeably.

2. It organized the evidence poorly, so poorly, that it is not difficult for one, in reading the Report, to lose sight of tee objectives.

3. It did not use a systematic approach in investigating various aspects of the problem.

4. It failed frequently to offer reasonable or meaningful derinitions of statistical and epidemiological terms. An outstanding example of this is given on page 3 of the critique.

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5. It was not altogether consistent in applying principles.

6. Its criteria for judging causation were not entirely realistic. In fact, with one exception, those criteria could be better described as criteria for ascertaining the value of a variable as a *diagnostic index*, a *predictor*, or both.

7. It engaged in a considerable amount of rationalization with respect to evidence which did not conform to the particular hypothesis which it had chosen to explore in detail. On the other hand, it appeared to be more convenient for the Committee to downgrade evidence which was consistent with another hypothesis than for it to change its policy and explore that hypothesis in detail as well.

8. Its Report is replete with redundancies. Indeed, there are instances in which the paraphrasing is such that one is left with the impression that new pieces of evidence were being introduced.

9. It did not distinguish between *primary* and *secondary* cancer of the lung, and such a distinction is essential, since cigarette smoking or not smoking is not assumed to be related to the occurrence of secondary cancer of the lung.

10. Not all pertinent scientific disciplines were represented on the Committee. For example, there was no psychiatrist, psychologist, sociologist, geneticist or radiologist on the Committee.

11. The Committee did not appear to be consistently aware of the fact that *self-selection* is the one known *factor* which cannot be controlled completely in any survey regardless of form. Self-selection may be characterized in the following hypothesis:

Even if cigarette smokers, as a group, did not smoke, there still would be a higher proportion of persons with *primary* cancer of the lung, say, among them than among non-smokers, as a group, since constitutionally they are more disposed to the disease. That, of course, is a statement of the *constitutional hypothesis*.

By taking all of these criticisms and others into consideration, and by exploring the constitutional hypothesis in much greater detail than did the Surgeon General's Committee, the author is able to conclude that there is strong reason to believe that the evidence appearing in the Report of the Surgeon General's Committee fits the *constitutional hypothesis* at least as well as it does the *cigarette hypothesis*. That alone would suggest that a causal significance cannot be attached to the relationships mentioned at the outset of the critique, i.e., to the relationship between cigarette smoking or not smoking and the occurrence of certain respiratory diseases and to the relationship between cigarette smoking or not smoking and the occurrence of coronary heart disease. (It is not feasible to conduct studies of the type which would force these relationships to disappear if they are not those of cause and effect). Finally, more research would be necessary to test *definitively* the strength of one hypothesis against that of the other, and that is how the author feels the situation with respect to smoking and health stands at the present.

DISCUSSION

W. G. COCHRAN. As the statistician on the Committee whose report Dr. Saiger has criticized, I am a little hesitant to enter the discussion. The Committee studied the evidence for a year, with great assistance from a large panel of expert consultants. The Committee's report has 387 pages, and received widespread distribution and publicity. Consequently, there is merit in the point of view that the Committee has had its say, and that when critiques appear, the interested bystander can read the critique and the Report and form his own opinion.

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Further, the problem of the relation between smoking and health is one on which new data are continuously accumulating, particularly data on females, of which relatively little was available to the Committee, and further person-years of experience in the prospective studies, which facilitate the type of control on more variables that Dr. Saiger and I both favour. The most interesting question is not what the state of the evidence was early in 1963, when the Committee study was in progress, but what it is now. This, of course, gets beyond the scope of Dr. Saiger's paper.

Nevertheless, I would like to comment, for two reasons. Dr. Saiger's references to the Committee's work are inaccurate in a number of respects. I would like to quote two examples, to reinforce my hope that those who are interested in his arguments will read the relevant part of the report. Secondly, the problem of appraising the self-selection or constitutional hypothesis — the main theme of Dr. Saiger's paper — is a challenging one for statisticians.

First as regards inaccuracies. On pp. 6—7 Dr. Saiger doubts the competence and ability of the 10 men, and particularly of the poor statistician, to cover the vast literature on this problem in the time used. He omits to tell you of the 189 persons and agencies used as expert consultants, through these are listed and their contributions described right at the beginning of the Report.

At the top of page 3, Dr. Saiger refers to the committee's definition of a cause as being "a significant, effectual, relationship between an agent and an associated disorder or disease in the host", and proceeds to ridicule such a definition. In fact, the Committee gave no formal definition of a cause, recognizing that cause and effect are complex ideas, but instead discussed on pp 20—21 their conception of causality. The sentence from which Dr. Saiger purports to be quoting reads as follows (p.21). "The word *cause* is the one in general usage in connection with matters considered in this study, and it is capable of conveying the notion of a significant, effectual, relationship between an agent and an associated disorder or disease in the host". The Report goes on at once to state: "no member of this Committee used the word *cause* in an absolute sense in the area of this study" and "all members shared a common conception of the multiple etiology of biological processes".

As regards the self-selection hypothesis, I agree with Dr. Saiger that a well-planned, long-term randomized experiment would be enlightening but is impracticable. In appraising this hypothesis from non-randomized data, what can one do? To quote some of the statistical evidence for males, the death rate at a given age increases steadily with the number of cigarettes smoked. For men of a given age who report smoking the same amount, the death rate increases with the number of years smoked. For men of a given age who previously smoked a given amount, the death rate is lower for those who have stopped than for those who have continued. In two groups of men of the same age who have stopped for the same length of time, the group which previously smoked more have the higher death rate. Dr. Saiger seems to think that the self-selection hypothesis can comfortably accomodate all these results and others which I could cite. My opinion is that it is being stretched very thin.

Secondly, one considers all studies in which differences in physique, habits, ancestry, psychological pattern and so on between cigarette smokers and non-smokers have been examined. Dr. Saiger mentions, as does the Report, a number of variables in which differences have been found in some studies. However, these differences are at most small differences between the means of two populations that overlap extensively.

Thirdly, in the prospective and retrospective studies, one adjusts for any variables other than smoking that are known or suspected to be related to the probability of dying. In the analyses leading to the Report, these adjustments were computed wherever the data allowed it. Except for age, for which adjustment is essential, these computations produced only slight changes in the mortality ratio. On page 13, in mentioning a seven — variable adjustment by Hammond, Dr. Saiger points out that the 7 did include important variables such a longevity of parents and grandparents, initial health status of the subject, marital status, and so on. Actually, Hammond already examined the effects of adjusting for each of these variables individually, again finding only slight changes in the mortality rbtio. From inspection of Hammond's data, my judgement was and is that the combination of variables would give essentially the same conclusion.

From all this, the Committees reached the judgement that self-selection could account for only a minor fraction of the observed difference in death rates. It felt in no position to put a precise figure, say 5% or 15%, on this fraction, and like Dr. Saiger, I look forward to seeing more data bearing on the constitutional hypothesis. I feel, however, that the extreme form of the constitutional hypothesis cannot be appraised by these methods. No matter for how many variables we adjust, the objection can be raised that the difference in death rates is due to some further variable not yet measured.

Finally, my opinion is that the new data that I have seen since 1963 do not weaken the main conclusions of the Report.

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V. G. PANSE. A sample survey cannot provide rigorous evidence of cause and effect relationships, irrespective of how many variables are controlled, since factors affecting observed phenomena are almost innumerable. At best, the results can indicate possible lines for further investigation. Some years back Prof. Fisher offered the hypothesis that persons who were genetically more prone to cancer developed a craving for smoking. Neither this nor any other hypothesis can be tested by sample survey. It requires experimentation by randomization of experimental units. Since this does not seem feasible when dealing with human beings, data obtained from experiments on laboratory animals should be very valuable ancillary evidence. Correlations observed in sample surveys should not be taken for cause and effect relationships but as indications which can be tested unequivocally only by experimentation.

G. L. SAIGER. Thank you, Prof. Cochran, for your comments. These are my comments in turn:

1. I should like to urge those who are interested in the problem of whether or not smoking affects health adversely to read the full text of my critique as well as the Report of the Surgeon General's Committee. One ought not to consider my summary, Prof. Cochran's comments and my rebuttal sufficient for the purpose of forming an opinion of his own.

2. Additional evidence *has* accumulated since the Report of the Surgeon General's Committee was first issued. That evidence cannot alter the methods employed by the Committee in arriving at its conclusions, the character of the Report itself nor the composition of the Committee as far as scientific disciplines are concerned. Depending on its quality, I am willing to accept the evidence on which the Report was based and the new evidence for the purpose of testing the strength of the cigarette hypothesis against that of the constitutional hypothesis. I am convinced that all such evidence, old and new, fits the constitutional hypothesis at least as well as it does the cigarette hypothesis.

In speaking of new evidence, Prof. Cochran fails to mention those studies whose results suggest that, exclusive of changes brought about by the disease itself, persons with cancer of the lung have characteristics which are not the same as those of other persons. That is important, since we already know that cigarette smokers differ from non-smokers constitutionally.

3. Prof. Cochran speaks in generalities about alleged inaccuracies in my critique with respect to the work of the Committee, and then proceeds to give examples of two:

a) It should be emphasized that the number of articles and other sources of information which the Surgeon General's Committee was reported to have reviewed exceeded 10 000, and most of the evidence contained in those articles and other sources of information was statistical in nature. Prof. Cochran states that 189 persons and agencies were used as expert consultants by the Committee. As far as I can determine, there were only 31 statisticians in that group, and not all of them would be classified as experts. Though Prof. Cochran had not expressed an opinion publicly on the problem of whether or not smoking affects health adversely before being called on to assist in weighing the evidence, can the same be said of the statistical consultants? My point is this: Some of the statistical evidence contained in the Report of the Committee is not the kind of evidence which a man without bias and of Prof. Cochran's competence would have accepted, I am certain, had he ascertained the value of that evidence himself.

b) Prof. Cochran claims that the Surgeon General's Committee gave no definition of "a cause". To support that claim, he refers to the following sentence on page 21 of the Report of the Committee:

"The word *cause* is the one in general usage in connection with matters considered in this study, and it is capable of conveying the notion of a significant, effectual, relationship between an agent and an associated disorder or disease in the host".

There is no doubt in my mind but that "a significant, effectual, relationship between an agent and an associated disorder or disease in the host" *is* the Committee's definition of "a cause", however Prof. Cochran may choose to interpret it. Obviously, such a definition deserves to be ridiculed. Obviously, such a definition needs to be qualified, and the Committee did that, at least in part, by stating that it did not use the word "cause" in an absolute sense and by expressing a concern for the concept of multiple causation.

4. Indeed, I do feel that evidence acquired in epidemiological surveys and appearing in the Report of the Surgeon General's Committee *is* consistent with the constitutional hypothesis. May I quote from pages 11 and 12 of my critique with respect to that hypothesis:

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From page 11—

"... Once a person's constitution is determined, so are his degree of disposition to the practice of cigarette smoking and his degree of disposition to the disease, and those degrees are highly and *positively* correlated".

From page 12—

"A low degree of disposition to the practice would be exemplified by the person who discontinues it freely after starting late in life and smoking two or three cigarettes per day for two years without inhaling".

That the Committee was confused with respect to the concept of "degree" as opposed to the concept of "kind" is well illustrated on page 10 of my critique. May I quote further:

"... The Surgeon General's Committee assumed that two distinct makeups were required to explore the constitutional hypothesis, one for cigarette smokers and one for non-smokers. But that assumption is neither realistic nor consistent with other observations on constitution made by the Committee. For example, the Committee did not expect to find all males among cigarette smokers and no males among non-smokers. Yet sex is a constitutional factor. In a similar fashion, it should not have expected to find all neurotics in one group and no neurotics in the other, nor even a much higher proportion of neurotics in one group than in the other".

5. Prof. Cochran states that constitutional differences between cigarette smokers and non-smokers are at most small differences. Presumably, he derived that opinion from an examination of single variables. It is not unusual, with biological variables, to observe a considerable amount of overlapping of distributions. I already have alluded to that possibility in the preceding paragraph. Furthermore, I was able to increase estimated distances between the groups significantly by forming combinations of variables. That was one basis for the statement in my critique that constitution more adequately would be represented by a combination of variables. That was one basis for the statement in my critique, and in my summary, that it appeared to be more convenient for the Surgeon General's Committee to downgrade evidence which was consistent with another hypothesis than for it to change its policy and explore that hypothesis in detail as well.

And what does the Report of the Surgeon General's Committee show? It shows that longevity of parents and grandparents could have an appreciable effect on the overall relative risk of dying among cigarette smokers, and that health status of the subject at the beginning of the survey, marital status, whether or not tranquilizers were being used and degree of exercise are highly related to the probability of dying, i.e., they are known *factors* of importance in the occurrence of death. It also shows that Hammond did not include those factors in a combination. Prof. Cochran confirms that observation in his comments.

Hammond did include other factors in a combination, however, and his results indicate that age and sex are not the only factors which should be controlled in exploring the constitutional hypothesis. (Note: The Surgeon General's Committee controlled age and sex only in arriving at its relative risks). Prof. Cochran and I both agree that studies should be conducted in the area of controlling progressively larger combinations of variables. The constitutional hypothesis does not specify that, in epidemiological surveys, the point can be reached where the relative risks of dying would estimate unity. (The only way in which self-selection can be controlled completely is by means of a long-term human experiment). There is a strong possibility, however, that they would approach unity. If they did, then the conclusions of the Surgeon General's Committee would be weakened further rather than strengthened. Therefore, the statement by Prof. Cochran that "no matter for how many variables we adjust, the objection can be raised that the difference in death rates is due to some further variable not yet measured" is grossly misleading. For the same reason, I cannot agree with Prof. Cochran that the problem of exploring the constitutional hypothesis is a challenging one for statisticians.

6. There is an important piece of evidence which Prof. Cochran, as a member of the Surgeon General's Committee, fails to explain: Why is it that primary cancer of the lung, histologically similar to that found in humans, can be produced in animals and with a variety of substances, but, as far as is known, not with condensates of cigarette smoke?

Prof. Cochran's comments and my rebuttal may have created some misunderstanding. Therefore, in closing, let me state my position as follows:

I am not an advocate of the constitutional hypothesis. The chief purpose of my critique is to determine whether or not the conclusions of the Surgeon General's Committee are justified. In examining the methods employed by the Committee in arriving at its conclusions, I find that it should have explored more than one hypothesis in detail and I offer, as a logical alternative, the constitutional hypothesis.

Though Prof. Cochran and I disagree on many points we apparently do not disagree on an important one, namely on the need for more research to test further (or *definitively*, as I call it) the strength of the cigarette hypothesis against that of the constitutional hypothesis.

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The U.S. veterans study also permitted the comparison of age-specific coronary heart disease mortality rates for ex-smokers and current cigarette smokers (table 2A). From these data, it appears that cessation of cigarette smoking is followed by a reduction in risk of coronary heart disease mortality as compared to those who continue to smoke cigarettes.

TABLE 2A.—*Annual death rate per 100,000 from coronary heart disease by age, cigarette-smoking status and number of cigarettes smoked per day, U.S. veterans study*

Number smoked per day[1]	45-54		55-64		65-74	
	Current cigarette smokers	Ex-smokers[2]	Current cigarette smokers	Ex-smokers[2]	Current cigarette smokers	Ex-smokers[2]
1 to 9	195	125	594	432	1,374	1,105
10 to 20	297	133	830	557	1,577	1,260
21 to 39	390	57	912	743	1,701	1,366
40+	502	.....	1,101	646	1,955	1,452

[1] This is the current rate of smoking for current cigarette smokers and the maximum rate attained for ex-cigarette smokers.
[2] Ex-smokers who stopped for reasons other than doctor's orders.
Source: U.S. veterans study (12).

The Hammond study findings summarized in table 3 are based on coronary heart disease deaths reported over a 4-year period among approximately 1 million persons (441,000 men and 563,000 women).

TABLE 3.—*Coronary heart disease mortality ratios among current cigarette smokers only, by amount smoked daily*

Age and sex	Non-smokers	Cigarettes smoked daily			
		Under 10	10-19	20-39	40+
Men:					
45 to 54	1.0	2.4	3.1	3.1	3.4
55 to 64	1.0	1.5	1.9	2.0	2.1
65 to 74	1.0	1.3	1.6	1.6	(1)
75 to 84	1.0	1.2	1.4	1.1	.....
Women:					
45 to 54	1.0	0.9	2.0	2.7	.....
55 to 64	1.0	1.3	1.6	2.0	.....
65 to 74	1.0	1.1	1.4	1.9	.....
75 to 84	1.0	.....	.....	.....	.....

[1] Expected deaths were less than 10.
Source: Hammond, E. C. (17).

Tables 3 and 4 show that both men and women who smoke cigarettes have relatively higher death rates from coronary heart disease than nonsmokers, although men have higher rates than women. For each sex and for each age group, the mortality ratios for coronary heart disease generally increase with increased intensity of cigarette smoking (table 3). The highest mortality ratios for both men and women are observed in the 45–54 year age-group: the coronary heart disease death rates among heavy smokers in this age group are three times the death rates for nonsmokers for both sexes. The mortality ratios for both men and women decrease with advancing age in each intensity category. This trend may reflect the effects of selective survival of smokers who have survived the elevated risks at younger ages of coronary heart disease and other diseases associated with cigarette smoking.

Another explanation of the decrease in mortality ratios with aging is that the effect of smoking, while substantial in increasing death rates, cannot be expected to be proportionate to all other causes of coronary heart disease as age advances. Considering the advanced degree of atherosclerosis generally found among nonsmokers over age 65, the deleterious effect of smoking is more appropriately represented by the excess in death rates among smokers. Table 4 below shows the observed death rates from coronary heart disease among persons studied by Hammond and classified by age, sex, and smoking status. Although the mortality ratios decreased with age, differences in death rates, which reflect the numbers of persons who die in each age group, increase. This could be interpreted to mean that, although relative to other factors, the role of cigarette smoking tends to diminish with advancing age, the number of excess deaths per 100,000 smokers continues to rise with advancing age.

TABLE 4.—*Age-specific death rates from coronary heart disease per 100,000 persons by age, sex, and smoking status*

Age and sex	Smokers of cigarettes only	Nonsmokers	Excess rate due to cigarettes[1]	Mortality ratio
Males:				
45 to 54	422	150	272	2.
55 to 64	976	542	434	1.
65 to 74	2,025	1,400	625	1.
75 to 84	3,871	3,132	739	1.
Females:				
45 to 54	66	33	33	2.
55 to 64	275	163	112	1.
65 to 74	911	653	258	1.
75+	2,349	1,973	376	1.

[1] Calculated from the data.
Source: Hammond, E. C. [(17), p. 143.]

The relative decrease in death rates from coronary heart disease associated with the cessation of cigarette smoking is illustrated in table 4A.

TABLE 4A.—*Coronary heart disease (men). Age-standardized death rates for ex-cigarette smokers with history of cigarette smoking only, by former number of cigarettes smoked per day and years since last cigarette smoking. Death rates for current cigarette smokers with history of cigarette smoking only and men who never smoked regularly are shown for comparison. Men aged 50–69*

Ex-cigarette smokers (years since last cigarette smoking)	Smoked 1–19 cigarettes a day			Smoked 20+ cigarettes a day		
	Number of men	Number of deaths	Death rate	Number of men	Number of deaths	Death rate
Under 1 year	749	27	[1] 1,005	2,244	77	[1] 1,070
1 to 4 years	1,844	51	718	5,435	195	1,093
5 to 9 years	1,770	45	725	5,803	152	732
10+ years	4,200	84	498	8,142	206	670
Total ex-smokers	8,569	210	635	21,624	630	813
Current cigarette smokers	22,808	781	947	56,358	1,895	1,020
Never smoked regularly	55,728	1,114	502	55,728	1,114	502

[1] Four or more but less than 10 deaths expected in some of the component 5-year age groups.
Source: Hammond, E. C. [(17), p. 144]

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Doll and Hill

In a prospective study by Doll and Hill (27) of mortality among British physicians whose smoking habits had been previously recorded, there were 1,060 deaths in the course of 10 years in which the underlying cause was coronary heart disease (27, table 1). The physician population under observation totaled 320,185 person-years. The CHD deaths were classified into three major subcategories: Group 1, comprising 35 CHD deaths in which an associated condition related to smoking, e.g., lung cancer, was recorded on the death certificate; Group 2, comprising 721 CHD deaths in which no other significant contributory cause of death was recorded on the death certificate; and Group 3, comprising 613 CHD deaths which were associated with some other contributory cause, including conditions known to predispose to coronary heart disease, e.g., hypertension, diabetes, and obesity. The CHD death rates for smokers and nonsmokers based only on Group 1 deaths, while subject to large variation, show the largest differentials (data not shown). Among smokers of 25 or more cigarettes daily, the age-adjusted CHD death rate was nearly eight times that in nonsmokers.

Based on Group 2 coronary heart disease deaths, presumably uncomplicated by any other significant disease, the mortality ratio of age-adjusted death rates among continuing cigarette smokers to nonsmokers is found to be 1.6, and for heavy smokers to nonsmokers the ratio is 2.0. However, as shown in table 5, the mortality differentials between smokers and nonsmokers are much larger at the younger ages.

TABLE 5.—*Mortality ratios for different types of coronary heart disease by smoking habits*

Age group	Group 2 CHD			Group 3 CHD		
	Non-smokers	Continuing cigarette smokers		Non-smokers	Continuing cigarette smokers	
		All amounts	25 or more per day		All amounts	25 or more per day
35 to 44	1.0	4.7	9.7	(2)	(2)	(2)
45 to 54	1.0	2.8	3.5	1.0	1.1	1.7
55 to 64	1.0	1.4	1.6	1.0	1.4	1.9
65 to 74	1.0	1.4	1.8	1.0	1.4	.8
75 to 84	1.0	1.1	2.0	1.0	.8	.2
85 plus	1.0	1.0	(2)	1.0	1.4	(2)
Age adjusted—All ages	1.0	1.6	2.0	1.0	1.1	.9

[1] See text for definitions.
[2] Not computable; too few deaths for computation because of so few deaths.
[3] Very few men in this category.

SOURCE: Data in above table based on values from Study of British Physicians, Table 2 (27).

The mortality ratios shown for Group 3 deaths, i.e., CHD deaths accompanied by some other complicating disease, suggest that, for all age groups combined, smokers do not have any special risk to this type of coronary death. However, smokers below the age of 65 appear to be at a somewhat greater risk, while no consistent differentials are observed among persons in the older age groups.

In summary, the study substantiates other mortality studies' findings that CHD mortality ratios (current cigarette smokers vs. nonsmokers) increase with the number of cigarettes smoked daily, that the ratios are highest in the age group 45–54, and that they decrease as age advances. Moreover, smoking apparently is associated with deaths from coronary heart disease among persons free of other serious disease states.

In a prospective study of California longshoremen, Borhani (17) reported on the mortality experience of more than 3,700 men observed for 10 years. Table 6, derived from his data, provides some additional insights on both the independent and the interaction effects of cigarette smoking.

Men 45–64 years of age who were heavy smokers experienced higher death rates from coronary heart disease than did nonsmokers independent of whether they were hypertensive or nonhypertensive.

TABLE 6.—*Mortality ratio from coronary heart disease among male hypertensives and nonhypertensives by smoking history and age*

Age group	Blood pressure status[1]	Non-smokers[2]	Heavy smokers[3]
45 to 54	Nonhypertensive	1.0	2.2
	Hypertensive	2.5	9.6
55 to 64	Nonhypertensive	1.0	3.5
	Hypertensive	5.9	9.4

[1] Hypertensives are defined as those having systolic blood pressure of [illegible] mm. Hg or over or diastolic blood pressure of 95 mm. Hg or over. Nonhypertensives are those having blood pressure readings less than the above or not recorded.
[2] Nonsmokers are those persons who, at the time of the study, were not smoking any cigarettes or less than 20 cigarettes per day.
[3] Smokers are those who smoked 20 or more per day.

SOURCE: Borhani, N. O., et al. (17).

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Prospective Study of British Physicians. The original articles of Doll and Hill contain important details which have been omitted from the 1967 document. Table 5 has grouped all amounts of cigarette smoking, whereas the original articles have specified the quantity from 1 to 14, 15 to 24 and 25+ cigarettes. "There is no clear gradient with number of cigarettes smoked" quoting from (25, 26) Doll and Hill.

Alternatively, cigarette smoking and coronary thrombosis may be related to one another only indirectly through some other factor. It may be, for example, that men with a raised serum cholesterol or of a particular physical constitution (Seltzer, 1963) or who tend to take little physical exercise also tend to take up cigarette smoking, and that these factors contribute to the production of the disease. Such a hypothesis is not, at first sight, unattractive, since the ratio of the mortality rate of smokers to non-smokers is relatively small. But it becomes difficult to accept when all the evidence is taken into account—namely, the much closer relationship at young ages, the increase in mortality with increased amount smoked, the difference between cigarette and pipe smoking and between inhaling and not inhaling, the reduction in mortality with increasing time after smoking has been stopped, and the many physiological effects of smoking on the cardiovascular system. In short, that cigarette smoking is a cause of coronary thrombosis is not, we think, proved; but it is the most reasonable interpretation of the available facts.

In short, we would conclude from these data that the only cardiovascular cause of mortality to show any association with smoking habits is coronary disease, unrelated to hypertension, and that even here the differences in rates are not very marked. The death rate of all smokers (*4.03*) is 23% higher than that of non-smokers (*3.31*), and this excess appears to be limited to the cigarette smokers (*4.39*, or 33% above the non-smokers, Table 18). There is certainly no clear gradient with number of cigarettes smoked, but the highest mortality is found among the heaviest smokers and there appears to be a fall in mortality on giving up smoking (Table 19). We examine these findings more closely in Table 20, which shows the age-specific death rates from coronary disease. These figures show that a rising gradient of mortality from non-smokers to heavy cigarette smokers is clearly present at ages under 65, doubtful at ages 65–74, and absent at age 75 years and over.

We have not sought clinical information about the large number of deaths in this cardiovascular group and consequently have not felt justified in trying to separate a group of deaths which might be ascribed to "cor pulmonale." We noted earlier that 55 cardiovascular deaths included a reference to chronic bronchitis on the death certificate (coronary thrombosis 24, myocardial degeneration 15, hypertension 2, other heart disease 4, and cerebrovascular accidents 10), and it was shown in Tables 16 and 17 that these deaths were closely associated with smoking. It is possible that in a few of them the primary cause was really chronic bronchitis—particularly perhaps among those attributed to myocardial degeneration or "other heart disease"—and that these constitute another cardiovascular group which is also associated with smoking. On the evidence available, however, this group would not appear to be large enough to have materially affected the results. Possibly most such deaths among doctors are attributed directly to chronic bronchitis.

TABLE 18.—*Standardized Death Rates from Cardiovascular Diseases*

Cause of Death		No. of Deaths	Death Rate per 1,000					
			All Men	Non-smokers	All Smokers	Cigarette Smokers	Mixed Smokers	Pipe or Cigar Smokers
Cerebrovascular accidents	(a)*	462	1·39	1·26	1·41	1·43	1·27	1·44
	(b)†	143	0·45	0·51	0·44	0·50	0·41	0·23
	All	605	1·84	1·76	1·85	1·93	1·71	1·67
Coronary disease	(a)*	1,287	3·97	3·31	4·05	4·39	3·87	3·15
	(b)†	89	0·29	0·30	0·33	0·36	0·37	0·21
	All	1,376	4·26	3·61	4·38	4·65	4·25	3·39
Myocardial degeneration		337	0·97	0·59	1·02	1·01	0·95	1·00
Hypertension		133	0·42	0·45	0·42	0·45	0·35	0·37
Other heart disease		135	0·41	0·41	0·41	0·42	0·43	0·33
Other cardiovascular diseases		135	0·41	0·41	0·41	0·45	0·38	0·35
Nephritis		43	0·13	0·09	0·14	0·14	0·13	0·12
Total		2,769	8·44	7·32	8·61	9·11	8·24	7·23
Total hypertensive		370	1·15	1·26	1·14	1·22	1·17	0·81

*(a) Without reference to hypertension on the death certificate.
†(b) Hypertension referred to on the death certificate.

TABLE 19.—*Standardized Death Rates from Cardiovascular Diseases in Relation to the Number of Cigarettes Smoked*

Cause of Death		Death Rate per 1,000				
		No. of Cigarettes Smoked Daily				Given Up Smoking Cigarettes
		1–14	15–24	25+	All Amounts	
Cerebrovascular accidents	(a)*	1·46	1·43	1·63	1·49	1·42
	(b)†	0·46	0·48	0·54	0·51	0·51
	All	1·93	1·91	2·23	2·00	1·93
Coronary disease	(a)*	4·35	4·28	4·97	4·57	3·73
	(b)†	0·29	0·29	0·18	0·28	0·19
	All	4·65	4·57	5·16	4·86	3·92
Myocardial degeneration		1·10	0·94	0·97	1·07	0·87
Hypertension		0·44	0·45	0·45	0·44	0·40
Other heart disease		0·32	0·39	0·21	0·41	0·41
Other cardiovascular diseases		0·41	0·45	0·42	0·54	0·25
Nephritis		0·16	0·14	0·29	0·17	0·09
Total		9·03	9·05	9·93	9·51	7·86
Total hypertensive		1·20	1·22	1·17	1·25	1·10

*(a) Without reference to hypertension on the death certificate.
†(b) Hypertension referred to on the death certificate.

TABLE 20.—*Death Rate from Coronary Thrombosis by Age**

Age in Years	No. of Deaths	Death Rate per 1,000				
		Non-smokers	Current Cigarette Smokers Smoking Daily			All Cigarette Smokers, Ex and Current
			1–14	15–24	25+	
35–44	36	0·11	0·41	0·49	1·50	0·61
45–54	149	1·12	1·95	3·43	2·73	2·61
55–64	319	4·91	6·41	7·03	8·41	7·20
65–74	369	10·83	16·44	13·04	17·59	14·69
75–84	314	21·20	21·22	15·34	17·20	19·15
85+	78	32·35	31·06	36·54	—†	35·05
All ages	1,267	3·31	4·36	4·28	4·97	4·30

*Includes all deaths attributed to coronary thrombosis, except those for which hypertension was mentioned as a contributory cause (V).
†Very small total number of man years at risk (27)—no deaths due to coronary thrombosis.

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An analysis was made by Schor (*86*) of 181 adult males who died from coronary heart disease generally less than 2 years after receiving a periodic health examination. The results of this study and those of Doll and Hill suggest that sudden death from previously undetected coronary heart disease frequently occurs among cigarette smokers. If this is true, it may, in part, account for the small differentials in the prevalence of coronary heart disease between smokers and nonsmokers observed in some morbidity prevalence surveys. As will be described in the following section, longitudinal, prospective morbidity studies also show that smokers are more likely to die from sudden attacks of coronary heart disease.

Coronary Heart Disease Morbidity*

In chapter 11 of the 1964 Surgeon General's Report, several prospective studies on the incidence of coronary heart disease (*24, 31, 78, 88*) established that smokers were subject to higher rates than nonsmokers. The relationship was reported to be more marked under 50 years of age than among older persons and appeared to be associated with myocardial infarction but not with angina pectoris. Since the 1964 report, recent findings from large-scale, on-going prospective studies have been reported, providing additional insight on the interaction between smoking and other important coronary heart disease risk factors. Current findings are summarized in the following pages including tables 7 to 13. Whenever possible, data are shown separately for findings related to angina pectoris and those pertaining to myocardial infarction, including sudden death attributed to coronary heart disease. Higgins (*50*) has drawn attention to the fact that "many factors may influence or be affected by smoking habits, and obscure those differences between smokers and nonsmokers which are directly related to the use of tobacco." In her review of the literature, Higgins identified differences between smokers and nonsmokers in genetically determined qualities (*23*), in physique (*77, 93*), in personality (*37, 47, 48, 65, 68, 69*), and in social, cultural, religious, and economic characteristics (*40, 49, 68, 84*).

*Also may include mortality data in this presentation.

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Sudden Deaths. This paragraph implies that sudden death occur more frequently among smokers, Schor et al. (86) specified one group of sudden deaths, i.e. those who die from coronary disease undetected. The incidence of sudden deaths of smokers compared to nonsmokers cannot be derived from the article. A portion of the Discussion is as follows:

> The person who dies from coronary heart disease which has escaped detection constitutes a special problem. In our population 42% were in this category. Our findings show that, by our present techniques, such a person more closely resembled his alive counterpart without evidence of heart disease than he did the person who died with the diagnosis of the disease. Furthermore, this person died somewhat sooner after his last examination than did the man in whom the disease had been identified. The lethal process can, therefore, be presumed to have been advanced at the time of examination. Clearly, new or improved methods will be required to distinguish this man from normal persons. Recent studies (2) suggest that differences may reside in social, personality, or other factors that are not now tested in the usual periodic health examination. The one finding that, in our study, distinguished this man from his living counterpart, was heavy cigarette smoking. Whether this, as such, is an important factor or simply a reflection of some other factor we are not in a position to say.

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Age

The effect of age on the incidence of coronary heart disease with regard to cigarette smoking is shown in table 7 based on recent data from the Framingham Study as yet unpublished.

TABLE 7.—*Incidence rates and morbidity ratios for coronary heart disease by age and smoking status of men 12-year experience, Framingham, Mass.*

Age	Incidence rates per 1,000		Excess rates per 1,000	Morbidity ratio	
	Non-smokers	Smokers	Smokers minus non-smokers	Non-smokers	Smokers
35 to 44	1.4	4.1	2.7	1.0	2.9
45 to 54	4.6	11.1	6.5	1.0	2.4
55 to 64	16.2	25.4	9.2	1.0	1.6

Source: U.S. Public Health Service, Framingham Study (95). (Updated 1967)

When the incidence rate of coronary heart disease among male nonsmokers between 35–44 years of age is compared with that among older nonsmokers, the rate is seen to triple every 10 years. This marked increase in incidence among nonsmokers reflects the effect of other important risk factors and perhaps accounts for the decrease in morbidity ratio as age advances. The independent effect of smoking on the incidence of coronary heart disease is believed to be more appropriately represented by the excess morbidity rates, which increase from 2.7 per 1,000 smokers in the age group 35–44 to 9.2 per 1,000 smokers 55–64 years of age.

High Blood Pressure

Although the inhalation of cigarette smoke is frequently accompanied by acute transient elevations in blood pressure, habitual smokers tend to have lower blood pressures than do nonsmokers (*48*). But, given the presence of high blood pressure in an individual, smoking acts as an additional risk factor for the development of coronary heart disease (*17, 28, 29, 50, 53, 55, 56, 96*). Both the independent and the combined effect of cigarette smoking is clearly shown in table 8 derived from the experience of the Framingham and Albany studies (*50*).

TABLE 8.—*Age-adjusted morbidity ratios for coronary heart disease among smokers and nonsmokers according to level of systolic blood pressure*

Systolic blood pressure	Nonsmokers of cigarettes	Cigarette smokers
Under 130 mm. Hg	1.0	2.1
130 mm. Hg and over	1.8	3.8

Source: 10-year Framingham and 6-year Albany experience (50).

High Serum Cholesterol

It is not now conclusively known if cigarette smoking by itself can cause increases in serum cholesterol. Dietary influences as well as endogenous production and elimination of cholesterol must be evaluated in greater detail with simultaneous analysis of the roles of other risk factors, including smoking. One study of a small population of twins in Sweden, as reported by Lundman (*67*), suggests that smoking monozygotic twins tend to have lower cholesterol levels than their nonsmoking control twins, although the differences are not statistically significant. Other studies suggest that smokers generally have higher serum cholesterol than nonsmokers (*13, 67, 88*). However, given the presence of high serum cholesterol, smoking increases the risk of coronary heart disease (*95, 96*).

The independent and synergistic effect of cigarette smoking is demonstrated by the data in table 9 derived from the combined experience of the Framingham and Albany studies (*50*).

TABLE 9.—*Age-adjusted morbidity ratios for coronary heart disease among smokers and nonsmokers according to level of serum cholesterol*

Serum cholesterol level	Nonsmokers of cigarettes	Cigarette smokers
Low[1]	1.0	1.8
High[1]	2.0	4.5

[1] "Low" is below median, "High" is above median value of serum cholesterol.
Source: 10-year Framingham and 6-year Albany experience (50).

(96) U.S. PUBLIC HEALTH SERVICE. The Framingham Heart Study. Habits and Coronary Heart Disease. Washington, U.S. Department of Health, Education, and Welfare, Public Health Service, Publication No. 1515, 1966.

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Smoking and hypercholesterolemia. This subject has been alluded to in the commentary of 1964 document, page 354a. There are several studies indicating that there is no relationship between smoking and cholesterol levels (page 207-210).

The cited article (13) Benson et al. does not show that smokers generally have higher serum cholesterol levels than nonsmokers. The Results quoted from the article are as follows:

> The mean serum cholesterol was also higher in urban men in both age groups (Table 1). Twenty-one per cent of the younger urban men and 12 per cent of the older urban men had serum cholesterol levels of greater than 260 mg per cent in contrast to 11 per cent of the younger and none of the older rural males.
>
> Urban men smoked less than their rural cohorts. The percentage of cigarette smokers in urban men was less in both age groups, but was statistically significant only in the younger age group (Table 1). However, there was a higher percentage of "heavy" (greater than one pack per day) cigarette smokers in the urban men in each age group (Table 1).

Table 1—Comparison of urban and rural males

	Age Group	Number of Subjects Urban	Number of Subjects Rural	Urban	Rural	p
Mean systolic and diastolic blood pressure (mmHg)	45-54	33	28	139/87	121/76	<0.001*
	55-64	17	16	154/90	127/76	<0.001*
Relative weight	45-54	33	28	107	98	<0.02†
	55-64	17	16	100	95	<0.03†
Mean serum cholesterol (mg/100cc)	45-54	33	28	231	211	<0.02†
	55-64	17	16	220	199	<0.10
Per cent cigarette smokers	45-54	33	28	42	86	<0.001†
	55-64	17	16	29	56	<0.12
Per cent "heavy" (greater than 1 pack/day) cigarette smokers	45-54	14‡	23‡	64	35	—
	55-64	5‡	9‡	80	55	—
Per cent "abnormal" electrocardiograms	45-54	33	28	15	7	<0.42
	55-64	16	16	6	12	<0.55
Mean hematocrit (%)	45-54	33	28	45	44	<0.42
	55-64	17	16	43	45	<0.11

* Statistically significant for both systolic and diastolic.
† Statistically significant.
‡ Total number who are present smokers.

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Pulmonary Function

The acute effects of cigarette smoking upon pulmonary function are expressed mainly through increase in airway resistance. The differences in pulmonary function between smokers and nonsmokers appear to be greater than can be accounted for by acute effects from a recently smoked cigarette (*30, 91*). The relationship of coronary heart disease to lowered pulmonary function as reflected by low vital capacity and cigarette smoking is observed in the data published by the National Institutes of Health based on the 12-year experience in Framingham (*36*). Morbidity ratios derived from this publication are shown in table 10.

TABLE 10.—*Age-adjusted morbidity ratios for coronary heart disease among smokers and nonsmokers according to level of vital capacity*

Vital capacity	Nonsmokers of cigarettes	Cigarette smokers
Under 3 liters	1.0	1.7
3 liters or more	1.7	2.4

Source: The Framingham heart study. (36).

Here again, the independent and combined effects of cigarette smoking are observed.

Physical Inactivity

A physically inactive or sedentary individual seems to run a higher risk of developing coronary heart disease (*33, 40, 41, 76*). Spain (*88*) reported that, in his prospective study of 3,000 men "* * * the relationship of occupational physical activity to smoking habits revealed that one of six sedentary workers were heavy smokers and one of five strenuous workers were heavy smokers." Weinblatt, in reporting the experience of the Health Insurance Plan of Greater New York (*160*) also found that a higher proportion (41.9 versus 33.0 percent) of cigarette smokers were classified in the "most active" physical activity category.

The independent and the combined effects between cigarette smoking and physical activity are shown in table 11. The morbidity ratios for myocardial infarctions are derived from published data.

TABLE 11.—*Age-adjusted morbidity ratios for myocardial infarctions among smokers and nonsmokers according to physical activity level*

Physical activity	Nonsmokers of cigarettes	Cigarette smokers
Most active	1.0	2.6
Least active	2.4	3.4

Source: Weinblatt, E. (160).

Socioenvironmental Stress

Since 1955, research on socioenvironmental stress in relation to coronary heart disease has increased greatly (*83, 92*). Among the factors studied that indicate a strong association with coronary heart disease incidence and prevalence is sociocultural mobility, that is, moving from one social setting to another. The interaction of this factor and cigarette smoking has been reported by Syme (*39, 91*) in both an urban and rural setting. Apparently in both areas cigarette smokers were more culturally mobile than nonsmokers. The independent effect of cigarette smoking on the incidence of coronary heart disease is shown in the morbidity ratios in table 12 derived from the North Dakota study (*91*).

TABLE 12.—*Age-adjusted morbidity ratios for coronary heart disease among smokers and nonsmokers according to sociocultural mobility status*

Sociocultural status	Never smoked cigarettes	Current and former cigarette smokers
Stable	1.0	1.5
Highly mobile	2.3	3.2

Source: North Dakota study. (91)

(91) SYME, S. L., HYMAN, M. M., ENTERLINE, P. E. Some social and cultural factors associated with the occurrence of coronary heart disease. Journal of Chronic Diseases (St. Louis) 17: 277-289, 1964.

(39) FOX, S. M., III, SELNNER, J. S. Physical activity and cardiovascular health. American Journal of Cardiology (New York) 14(6): 731-746, December 1964.

(40) FRANK, C. W., WEINBLATT, E., SHAPIRO, S., SAGER, R. V. Myocardial infarcation in men. Role of physical activity and smoking in incidence and mortality. Journal of the American Medical Association (Chicago) 198(12): 1241-1245, Dec. 19, 1966.

(41) FRANK, C. W., WEINBLATT, E., SHAPIRO, S., SAGER, R. V. Physical inactivity as a lethal factor in myocardial infarction among men. Circulation; Journal of the American Heart Association (New York) 34: 1022-1033, December 1966.

(76) PAFFENBARGER, R. S., JR., WOLF, P. A., NOTKIN, J., THORNE, M. C. Chronic disease in former college students. I. Early precursors of fatal coronary heart disease. American Journal of Epidemiology (Baltimore) 83(2): 314-328, 1966.

(160) WEINBLATT, E. Personal communication. Health Insurance Plan of Greater New York, Apr. 17, 1967.

(83) RUSSEK, H. I. Stress, tobacco, and coronary disease in North American professional groups. Survey of 12,000 men in 14 occupational groups. Journal of the American Medical Association (Chicago) 192(3): 189-194, April 19, 1965.

(92) SYME, S. L., BREWER, L. G., editors. Social stress and cardiovascular disease. Proceedings of the National Workshop Conference on Socio-environmental Stress and Cardiovascular Disease, Phoenix, Ariz., Feb. 14 to 16, 1966. The Milbank Memorial Fund Quarterly (New York) 45 (No. 2, pt. 2): 1-192, April 1967.

(39) SYME, S. L., BOSHANE, N. O., BUTCHLEY, R. W. Cultural mobility and coronary heart disease in an urban area. American Journal of Epidemiology (Baltimore) 83(3): 334-346, November 1966.

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Pulmonary Function in Smokers. The cited articles (50, 91, 96) do not relate to a comparison of pulmonary function between smokers and nonsmokers. However, this topic was investigated by (21) Chevalier et al. in an earlier publication (1963), and by (61) Krumholz et al., 1964. These articles are quoted in the 1967 document in relation to exercise (page 367). These investigators did not find any significant difference in vital capacity or airway resistance between smokers and nonsmokers. The Results from Chevalier et al (J Appl Physiol 18: 357-360, 1963) and Krumholz et al. (Ann Intern Med 60: 603-610, 1964) are as follows:

TABLE 2. *Pulmonary characteristics of subjects*

	Smokers	Nonsmokers
Vital capacity, ml	5,009 ± 627	3,384 ± 4[illegible]
Total lung capacity, ml	6,930 ± 838	7,185 ± [illegible]
RV/TLC, %	26.1 ± 4.9	26.2 ± 5.4
Airway resistance, cm H_2O liter sec	1.82 ± .61	1.69 ± 5[illegible]
1-Sec timed vital capacity, % of total	84.6 ± 8	89.5 ± 6
Max. expiratory flow rate, liters/min	596 ± 84	600 ± 6[illegible]
Max. breathing capacity, % of predicted normal	101.7 ± 18.3	98.9 ± 8[illegible]

Values are expressed as the mean ±1 SD. There is no significant difference ($P > .05$) between mean values for the two groups.

Subjects	Inspiratory* Capacity	Inspiratory Reserve Volume	Expiratory Reserve Volume	Tidal Volume	Vital Capacity	Functional Residual Capacity	Residual Volume	Total Lung Capacity	Residual Volume/ Total Lung Capacity	Maximal Voluntary Ventilation	Maximum Expiratory Flow Rate	Airway Resistance
	ml	*ml*	*ml*	*ml*	*ml*	*ml*	*ml*	*ml*	%	*liter/min*	*liter/min*	*cm H₂O/ liter/sec*
Smokers												
1	3,170	2,400	1,420	770	4,590	2,600	1,180	5,770	20	147	420	1.27
2	2,760	2,160	2,430	600	5,190	4,700	2,270	7,460	30	142	570	.62
3	3,160	2,180	2,050	980	5,220	4,400	2,350	7,570	31	168	680	1.09
4	2,570	1,920	2,040	650	4,610	3,900	1,860	6,470	29	141	550	1.21
5	3,220	2,470	2,170	750	5,380	3,600	1,430	6,810	21	168	650	.97
6	2,940	2,110	2,580	830	5,520	4,600	2,020	7,540	26	184	660	1.04
7	2,180	1,490	2,600	690	4,790	3,400	800	5,590	14	142	520	.85
8	3,800	2,710	890	1,090	4,690	1,800	910	5,600	16	173	550	.83
9	3,590	2,540	1,920	1,050	5,540	3,500	1,580	7,120	22	206	710	1.03
Mean:	3,040±500†	2,220±370	2,010±560	820±80	5,060±380	3,610±950	1,600±570	6,650±690	23±6	163±24	590±90	.98±.19
Nonsmokers												
1	3,710	2,830	2,780	880	6,490	5,200	2,420	8,910	—	154	570	.90
2	3,650	1,950	1,400	1,700	5,050	3,200	1,800	6,850	26	203	610	1.02
3	3,500	2,540	1,560	960	5,050	3,500	1,940	6,990	28	177	640	.71
4	3,370	2,820	3,400	550	6,780	6,700	3,300	10,080	33	169	640	1.13
5	3,630	3,140	2,550	490	6,190	4,100	1,550	7,740	20	146	600	.83
6	3,180	2,050	1,910	1,130	5,100	3,800	1,890	6,990	27	161	560	.74
7	4,220	3,300	2,160	920	6,380	3,800	1,640	8,020	20	166	480	1.03
8	4,030	3,400	2,010	630	6,050	3,600	1,590	7,640	21	161	640	.53
9	3,260	1,750	1,120	1,500	4,370	4,400	3,280	7,650	43	123	510	.82
Mean:	3,610±350	2,640±610	2,100±720	970±390	5,720±830	4,260±1,090	2,160±690	7,870±1,060	25±13	162±22	580±60	.86±.19
P	>.05	<.10	>.80	>.50	<.05	>.80	>.10	<.05	>.50	>.50	>.30	>.20

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Personality Type

Various investigators have long suspected a possible pathogenetic role of the central nervous system in coronary heart disease (*35*). In a series of reports, Rosenman (*81, 82*) and Jenkins (*51*) have described a personality pattern or overt emotional complex which, while associated with other known risk factors, appears to predict coronary heart disease more effectively than do other risk factors. This emotional complex, "which they have termed Behavior Pattern Type A, is composed of an enhanced competitiveness, drive, aggressiveness and hostility, and an excessive sense of time urgency." Recent unpublished data based upon prospective observation of more than 3,000 men for a 4½-year period (*51*) discloses that smokers have a higher percentage (54 versus 47 percent) of type A persons among them. Moreover, the incidence of coronary heart disease is shown to be related independently to both smoking status and personality type. Morbidity ratios, derived from the incidence data, are shown in table 13 which clearly demonstrates the independent effects of cigarette smoking and its interaction with personality characteristics.

TABLE 13.—*Morbidity ratios of cigarette smokers as compared to nonsmokers by personality type*

Personality type	Nonsmokers of cigarettes	Cigarette smokers
Behavior type B	1.0	2.0
Behavior type A	2.5	4.4

SOURCE: Unpublished data from Western Collaborative Group Study, San Francisco, Calif. (*51*).

Multiple-Risk Factors

The method of analysis traditionally employed by epidemiologists, that of the comparison of rates for multiple cross-classifications of the data, generally requires a large study population at relatively high incidence of significant events. Since coronary heart disease incidence rates are low and study populations are necessarily small because of practical and practicable limitations, definitive analysis of the independence and interaction between risk factors have generally been restricted to two factors at a time. Truett (*95*) applied a multiple logistic function proposed by Cornfield to investigate the independent effect on the incidence of coronary heart disease of seven risk factors: Age, serum cholesterol, systolic blood pressure, relative weight, hemoglobin, cigarettes per day, and ECG abnormalities. The method was used in the analysis of data compiled in the Framingham study during a 12-year period. A discriminant function coefficient was computed for each risk factor. These coefficients represent the relative importance of each factor with respect to the other six factors in the development of coronary heart disease. While theoretical considerations underlying the logistic risk function are not fully satisfied by the actual data, the approximation given by the function to observed rates is very good.

Consequently, Truett and Cornfield believe that the present computations permit the conclusion that "the most important risk factors, aside from age itself, are cholesterol, cigarette smoking, ECG abnormality, and blood pressure" (*95*).

(35) EPSTEIN, F. H. The epidemiology of coronary heart disease: A review. Journal of Chronic Diseases (St. Louis) 18(5): 735–771, August 19[illegible].

(81) ROSENMAN, R. H., FRIEDMAN, M., JENKINS, D., STRAUS, R., WURM, M., KOSITCHEK, R. The prediction of immunity to coronary heart disease. Journal of the American Medical Association (Chicago) 198(11): 1130–1102, Dec. 12, 1966.

(82) ROSENMAN, R. H., FRIEDMAN, M., STRAUS, R., WURM, M., KOSITCHEK, R., HAHN, W., WERTHESSEN, N. T. A predictive study of coronary heart disease. Journal of the American Medical Association (Chicago) 189(1): 15–22, July 6, 1964.

(51) JENKINS, C. D. Personal communication. The University of North Carolina, Chapel Hill, Apr. 10, 1967.

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Manifestation of Coronary Heart Disease

Coronary heart disease is essentially comprised of three major manifestations or subcategories:

1. Fatal myocardial infarctions, including sudden deaths attributed to coronary heart disease;
2. Nonfatal myocardial infarction; and
3. Angina pectoris.

Generally, investigators in their analysis of the relationship of risk factors to the incidence of coronary heart disease have not subdivided the observed coronary events into the three major subcategories primarily because the paucity of events in each category did not permit definitive conclusions on any differences observed. However, the pooling of data from some of the larger prospective studies holds promise of a more complete analysis of the independent and synergistic effects of each risk factor on each of the subcategories of coronary disease. Findings from these analyses might provide some insights into the underlying pathophysiological mechanisms through which a risk factor operates. The pooled data from the Albany and Framingham studies and data from the HIP study include the observed associations of cigarette smoking with each of the three major manifestations. Morbidity ratios have been derived from these studies and are presented in table 14.

TABLE 14.—*Age-adjusted morbidity ratios for subcategories of coronary heart disease among smokers and nonsmokers*

Disease category	Framingham-Albany		Health insurance plan	
	Non-smokers of cigarettes	Cigarette smokers	Non-smokers of cigarettes	Cigarette smokers
Fatal myocardial infarction	1.0	2.4	1.0	2.1
Non-fatal myocardial infarction	1.0	2.3	1.0	1.8
Angina pectoris	1.0	1.1	1.0	1.7

SOURCE: Second Report of the Combined Experience from Albany and Framingham Studies (2). Unpublished Data from Health Insurance Plan Study (36).

The association of cigarette smoking to angina pectoris is not a consistent one. A clear-cut association was found in the Health Insurance Plan Study (ratio of 1.7); a similar association is also found in unpublished data from Framingham considered separately. However, no association between cigarette smoking and the incidence of angina pectoris was found in the Albany experience. Cederlof (*19*), in his analysis of prevalence data on angina pectoris obtained by questionnaire, found no statistically significant difference in prevalence rates between 453 monozygotic twin pairs with dissimilar smoking habits. In a larger study of about 9,000 persons from the twin register where genetic factors were uncontrolled, Cederlof (*12, 20*) did find a significantly higher prevalence of angina pectoris among smokers than nonsmokers, particularly in men (ratio of 1.6) (*67*).

Friedman (*42*) and Epstein (*36*) have clearly described the inherent biases in prevalence studies which may lead to findings of risk gradients that are different from those obtained in prospective incidence studies. One of these limitations is that fatal cases are underrepresented in a prevalence survey. Thus, since it appears that cigarette smoking is more closely related to the incidence of fatal myocardial infarctions than to other forms of coronary heart disease, it is expected that morbidity ratios derived from prevalence surveys would be lower than those computed from incidence data. With these restrictions in mind, Russek (*83*) in a survey of 12,000 men in 14 occupational groups found that the morbidity ratio of coronary heart disease prevalence among cigarette smokers was as high as 1.8. In contrast, in a study of 77 identical and 89 fraternal twins in Sweden, comparing smokers with their respective nonsmoking twins, Lundman (*67*) reported no excess prevalence of overt or silent coronary heart disease. However, the prevalence of these conditions, as Lundman concluded, "was too low to permit of definitive conclusions."

(19) Cederlof, R., Friberg, L., Jonsson, E., Kaij, L. Morbidity among monozygotic twins. Archives of Environmental Health (Chicago) 10(2): 346–350. February 1965.

(20) Cederlof, R. Friberg, L., Jonsson, E., Kaij, L. Respiratory symptoms and "angina pectoris" in twins with reference to smoking habits. Archives of Environmental Health (Chicago) 13(6): 725–737, December 1966.

(42) Friedman, G. D. Cigarette smoking and geographic variation in coronary heart disease mortality in the United States. Presented at Conference on Epidemiology of Cardiovascular Disease, American Heart Association, Chicago, Illinois, Feb. 3, 1967. [Unpublished.] 23 pp.

(36) Epstein, F. H. Some uses of prospective observations in the Tecumseh Community Health Study. Proceedings of the Royal Society of Medicine (London) 60: 56–60, January 1967.

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Twin Registry. This paragraph omits the significance of investigation of twins. The two sentences are correct but the significance is not discussed for the benefit of the general reader. A portion of the Conclusions of (20) Cederlof et al. is as follows:

/ The results obtained from group A, including only *one* twin from each pair, regardless of smoking habits, are, from the constitutional point of view, as heterogeneous as "normal material." These results reveal a marked association between smoking and symptoms. Thus, "angina pectoris" occurred throughout, to a greater extent among smokers than among nonsmokers, as did the different degrees of bronchial symptoms.

In regard to respiratory symptoms, the findings are fully in accord with previously reported experience.[1]

The question of hypermorbidity among smokers in regard to coronary disease has not received the same unanimous answer in published investigations. Extensive prospective studies of mortality from coronary disease, however, point unanimously to a connection with smoking.[17-21] As for morbidity in angina pectoris among smokers, an early report from the Framingham study[22] showed data that suggested an increased risk among men who smoked over 20 cigarettes per day. Later experience gained from the combined Albany and Framingham studies[20] have not verified an increased incidence of angina pectoris among smokers. A report published by the Health Insurance Plan of Greater New York on the incidence and prognosis of coronary disease found a clear hypermorbidity in angina pectoris among male smokers but not among women.[21]

Our material revealed a clear hypermorbidity in "angina pectoris" among male smokers in the series where genetic factors were uncontrolled (group A). A corresponding hypermorbidity could not be ascertained, however, when intrapair comparisons were made between smoker and nonsmoker in discordant twin groups. This difference in morbidity between the groups cannot be accounted for by differences in degree of exposure to tobacco. This is shown by the factual data concerning tobacco consumption and by the fact that the same degree of hypermorbidity was found in smokers' respiratory symptoms. Therefore, it seems highly probable that factors other than exposure to tobacco were of decisive importance. One such possible factor could lie in the fact that the smokers in group A tended more than those in the B groups to be town dwellers. However, investigations carried out to date make such an interpretation highly improbable.[23]

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Cardiovascular Response to Smoking and/or Nicotine

As noted in the Surgeon General's 1964 Report, nicotine has definite physiologic effects on the cardiovascular system of experimental animals and of man. These include increases in heart rate, systemic arterial pressure, cardiac output, stroke volume, and velocity of myocardial contraction, all resulting in an increased myocardial tissue oxygen demand (*16*). Coronary blood flow studies will be reported in the next section under a separate subheading. These effects parallel those observed with catecholamines (epinephrine and norepinephrine). The effects can be blocked by the injection of tetraethylammonium chloride and markedly reduced by adrenalectomy (*22*). Nicotine has been repeatedly shown to release endogenous catecholamines (*57, 58, 59, 60, 102*). However, the mechanism by which nicotine affects the cardiovascular system is more complex than the release of catecholamines from the adrenal medulla. Direct and indirect (via the carotid body and other chemoreceptors) stimulation of the vasomotor center, stimulation of sympathetic ganglia, release of norepinephrine from local stores, and release of antidiuretic hormone are included among other postulated mechanisms of action involved in nicotine's effect on the cardiovascular system (*16, 63, 85*).

Coronary Blood Flow in Normal Subjects

The action of smoking and/or nicotine on the coronary blood flow of normal human subjects has not yet been definitively established, but apparently normal subjects can increase their coronary blood flows sufficiently to maintain a compensatory blood supply to the myocardium despite the increased myocardial tissue demand for oxygen caused by cigarette smoking. Earlier findings of increased coronary blood flow in normal men, in response to cigarette smoking (*11*), were not reproduced in a more recent study (*76*). In this latter study, although a trend towards a slight increase in coronary blood flow was observed in the particular normal persons studied, it was not significant.

Direct injection of nicotine into the left coronary artery of dogs under conditions of constant flow rate resulted in increased coronary vascular resistance (*38, 64*). This response could be reduced by vagal nerve stimulation or prior administration of acetylcholine; an immediate increase in cardiac contractile force was also observed that could be similarly reduced. It was concluded that these responses to nicotine resulted from sympathetic nervous system activity or from the release of catecholamines by myocardial chromaffin tissue (*64*).

Blood from the smoke-exposed lung tissue of dogs, directly perfused into the coronary artery, failed to increase coronary resistance (*33*). This effect was thought to be secondary to that of histamine, known to act as a coronary vasodilator, which apparently is released from the lung tissue of dogs during their exposure to smoke (*8*).

When blood from the smoke-exposed lung was perfused through the systemic circulation of dogs while the coronaries were being perfused with non-smoke-exposed blood, the typical release of catecholamines occurred with many of the usual effects on cardiovascular parameters except that the coronary vascular resistance increased under these experimental conditions, apparently due to the increased activity of the sympathetic nervous system (*38*).

Since it is well known that exposing dogs to cigarette smoke without isolating and separately perfusing the coronary circulation normally results in an increase of the coronary blood flow (*38*), the manipulation of experimental conditions as described suggests that there is a masking effect by the catecholamines on nicotine's direct action on the coronary circulation (*38*).

These studies may relate, by analogy, to humans and indicate that smoking, in "normal" individuals, may produce at least two actions that can affect coronary blood flow: (1) a decrease in coronary blood flow by a possible direct action of nicotine on the coronary circulation (demonstrated in dogs), and (2) an increase in coronary blood flow as the usual resultant of varying responses to the intermediating action of catecholamines and other physiologic processes (demonstrated in both animals and humans).

(16) Bing, R. J., Cohen, A., Buechner, C. Tobacco alkaloids and circulation. *In:* Tobacco Alkaloids and Related Compounds. Proceedings of the 1st International Symposium held at the Wenner-Gren Center, Stockholm, February 1964: 1965. Pp. 211–231.

(22) Chiang, T. S., Leaders, F. E. Cardiostimulatory responses to vagal stimulation, nicotine, and tyramine. American Journal of Physiology (Washington) 211(6): 1413–1416, December 1966.

(57) Kershbaum, A., Bellet, S. Cigarette smoking and blood lipids. Journal of the American Medical Association (Chicago) 197(1): 52–56, Jan. 4, 1966.

(58) Kershbaum, A., Bellet, S. Smoking as a factor in atherosclerosis. Geriatrics (Minneapolis) 21(12): 155–170, December 1966.

(59) Kershbaum, A., Bellet, S., Jimenez, J., Peinado, L. J. Differences in effects of cigar and cigarette smoking on free fatty acid mobilization and catecholamine excretion. Journal of the American Medical Association (Chicago) 195(13): 1095–1098, Mar. 28, 1966.

(60) Krumholz, R. A. Pulmonary membrane diffusing capacity and pulmonary capillary blood volume: An appraisal of their clinical usefulness. American Review of Respiratory Diseases (Baltimore) 94(2): 195–200, August 1966.

(102) Westfall, T. C., Cipollone, P. B., Edmundowicz, A. C. Influence of propranolol on hemodynamic changes and plasma catecholamine levels following cigarette smoking and nicotine. Proceedings of the Society for Experimental Biology and Medicine (New York) 123: 174–179, 1966.

(63) Larson, R. K., Fukuda, P., Murray, J. F. Systemic and pulmonary vascular effects of nicotine in anesthetized dogs. American Review of Respiratory Diseases (Baltimore) 91(4): 550–564, April 1965.

(85) Samanek, M., Aviado, D. M. Cardiopulmonary effects of tobacco and related substances. III. Pulmonary vascular effects of cigarette smoke and nicotine. Archives of Environmental Health (Chicago) 12(6): 727–732, June 1966.

(11) Barreron, L. M., Jr., Ehmke, D., Gonzalez, F., Castellanos, F. A., Siegel, A., Pino, R. J. Effect of cigarette smoking on coronary blood flow and myocardial metabolism. Circulation; Journal of the American Heart Association (New York) 15: 251–257, 1957.

(38) Folle, L. E., Samanek, M., Aviado, D. M. Cardiopulmonary effects of tobacco and related substances. II. Coronary vascular effects of cigarette smoke and nicotine. Archives of Environmental Health (Chicago) 12(6): 712–716, June 1966.

(64) Leaders, F. E., Long, J. P. Action of nicotine on coronary vascular resistance in dogs. American Journal of Physiology (Washington) 213(4): 621–625, October 1967.

(8) Aviado, D. M., Samanek, M., Folle, L. E. Cardiopulmonary effects of tobacco and related substances. I. The release of histamine during inhalation of cigarette smoke and anoxemia in the heart-lung and lung-perfusion preparation. Archives of Environmental Health (Chicago) 12(6): 703–724, June 1966.

(1) Ashby, P., Daley, A. M., Millar, J. H. D. Smoking and platelet stickiness. Lancet (London) 2: 158–159, July 21, 1965.

(2) Astrup, P. An abnormality in the oxygen-dissociation curve of blood in patients with Buerger's disease and patients with peripheral arteriosclerosis. Lancet (London) 2: 1152–1154, Nov. 26, 1966.

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Cigarette smoke on coronary vascular resistance. The interpretation of the perfusion experiments by (8) Aviado et al and (38) Folle et al is not complete. The authors mention a second explanation in that the amount of nicotine absorbed in the lungs is not sufficient to influence the coronary vessels. The quotation from Folle et al is as follows:

> The perfused coronary artery behaved in the following manner: no immediate change when blood exposed to cigarette smoke was perfused into the coronary artery but an increase in coronary vascular resistance when nicotine was injected directly into the vessel. There are two possible explanations for this discrepancy: (*a*) that the amount of nicotine absorbed from the left lower lobe was less than the 1μg/kg injected directly into the perfused artery; or (*b*) that blood exposed to cigarette smoke did not act in the same manner as pure nicotine. In regard to the latter possibility, nicotine may be in the blood in sufficient quantities but there was an additional amount of substance released which antagonizes the primary actions of nicotine. Such a substance may be histamine which is known to reduce coronary vascular resistance,[23] and this may serve to reduce any effect of nicotine. These possibilities can be verified by determination of nicotine in the blood. Until a sensitive method becomes available, it is important to question the exclusive use of nicotine in the understanding of the coronary effects of tobacco.
>
> The systemic absorption of substances from the lungs exposed to cigarette smoke initiated stimulation of the sympathetic nervous system with an elevation in aortic blood pressure and positive inotropic action on the heart muscle. The latter was accompanied by an elevation in coronary vascular resistance, although the perfusing blood was not exposed to cigarette smoke. Both the changes in coronary vascular resistance and myocardial contractility are indications of generalized increase of sympathetic nervous activity. If the coronary artery was not perfused, the coronary vasomotor effect would have been masked by an actual elevation in aortic pressure and the entrance of catecholamines released from the adrenal medulla so that the end result would have been an actual increase in coronary blood flow. This conforms to the general conclusion in an earlier paper[24] that the cardiac effects of tobacco arise almost entirely from the extracardiac actions of smoking instead of a direct response of the heart.

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Coronary Blood Flow in Subjects with Coronary Heart Disease

The effect of cigarette smoking on coronary blood flow was studied in patients with coronary heart disease (*79*). As was seen in normal subjects, significant increases in heart rate, arterial pressure, and cardiac output were noted. In contrast to the normal individuals studied, patients with coronary heart disease distinctly showed a much less significant compensatory increase in their coronary blood flows. These results were confirmed by a later study (*16*), using the Rubidium 84 method to estimate coronary blood flow. This study also showed that in the coronary patients studied, there was no adequate compensatory increase in coronary blood flow to meet the increased myocardial tissue demand for oxygen. Coronary blood flow apparently decreased as a result of cigarette smoking, in this particular study group of coronary patients. Although the decreases noted were not marked, they were statistically significant, and indicated that a difference existed between these coronary patients as compared to the normal subjects studied.

A difference in the coronary blood flow response to nitroglycerine has also been demonstrated in normal subjects compared to subjects with coronary heart disease. This was shown in studies using the nitrous oxide (*18*, *44*) and the Rubidium 84 (*15*) methods to measure coronary blood flow. In response to nitroglycerine the normal individuals generally increased their coronary blood flow significantly, but the coronary patients generally did not.

Animal studies have also demonstrated the decreased ability of atherosclerotic coronary arteries to increase coronary blood flow, as compared to the coronary arteries in normal animals (*94*). Dogs with experimentally produced coronary artery insufficiency also show this decreased ability (*12*). Similar differences between animals with normal coronary arteries as compared to atherosclerotic coronary arteries have been demonstrated in response to ergonovine (*80*).

The above studies indicate that the effect of nicotine upon the cardiovascular system, mediated in part by the action of released catecholamines, is generally to increase heart rate and cardiac output, and to raise systemic arterial pressure temporarily. Findings concerning the effect of nicotine on coronary blood flow are presently thought to be largely due to the indirect effects of nicotine upon the cardiovascular system. Other animal studies indicate that there may be a direct action of nicotine on the coronary vasculature to increase coronary vascular resistance, thus tending to reduce coronary blood flow. There are no human studies on the direct action of nicotine by itself on the coronary vasculature; such studies, involving the direct injection of nicotine into diseased human coronary arteries, might be dangerous. Normal individuals apparently can increase their coronary blood flows to compensate for the increased myocardial tissue oxygen demand, but apparently some patients with coronary heart disease cannot, as shown by their response to smoking.

Thus some patients with coronary heart disease may be at a particular disadvantage when smoking and under other stresses since their coronary arteries apparently cannot dilate to supply blood flow adequate to meet the increased oxygen demand associated with nicotine-induced catecholamine release. The interaction of the above effect with recent findings concerning carbon monoxide, described in the next section, may be especially important in those individuals with coronary heart disease. The present studies indicate that the effect of cigarette smoking on coronary blood flow, in the presence of preexisting coronary heart disease, may, in part, contribute to the increased incidence of acute myocardial infarctions that have been observed to be associated with cigarette smoking. No relationship between the smoking effect on coronary blood flow and the pathogenesis of coronary atherosclerosis per se is presently suggested. Additional research is needed.

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Carbon Monoxide Effect

The gaseous phase of cigarette smoke contains about 4 percent carbon monoxide. This quantity can increase the levels of carboxyhemoglobin saturation of cigarette smokers from 2 percent to 10 percent (*21*). The average nonsmoker, depending on environmental exposure, usually has less than 2 percent carboxyhemoglobin saturation (*10*). Since smokers of one pack or more a day may have chronically elevated carboxyhemoglobin levels of more than 4 percent (*9*), there may be appreciable differences in the carboxyhemoglobin levels between some heavy cigarette smokers and nonsmokers.

In addition to displacing oxyhemoglobin, carbon monoxide effects a shift in the oxygen-hemoglobin dissociation curve (*2, 3, 4 5, 6*). This may result in a decreased release of oxygen at the tissue level. A series of studies (*61, 62*) has been performed on young adults to analyze the effect of cigarette smoking on carboxyhemoglobin levels, and the consequent effect on some parameters of cardiopulmonary function. An increased post exercise oxygen debt was observed after cigarette smoking as compared to controls. This, in part, may reflect not only ventilatory disturbances but also a decreased supply of oxygen in the blood due to the carbon monoxide effect, resulting in less available oxygen to meet the increased tissue demand. Similar post-exercise oxygen debts have been noted after inhalation of enough carbon monoxide to produce comparable blood levels of carboxyhemoglobin (*21*).

The consequence of the smoking/carbon monoxide effect appears to be especially important in the myocardium where relatively more oxygen is normally extracted from the coronary circulation as compared to other organ systems. (Coronary venous blood usually has an oxygen saturation of less than 25 percent, whereas blood leaving some other organs is about 75 percent saturated with oxygen (*45*).)

Dogs were exposed to carbon monoxide to elevate their carboxyhemoglobin saturation levels (*9*). In response to inhalation of carbon monoxide there was an increase in coronary blood flow but a decrease in coronary arterial-venous oxygen differences. Patients with coronary heart disease were also studied following inhalation of enough carbon monoxide to elevate their carboxyhemoglobin saturation levels to the range of 5 to 12 percent (*9*). In response to carbon monoxide there was generally an increase in the cardiac output and the coronary blood flow in most of the patients. While the systemic arterial-venous oxygen differences varied, either increasing or decreasing, the coronary arterial-venous oxygen differences decreased, indicating a decreased oxygen extraction by the myocardial tissue despite the myocardium's increased demand for oxygen. These decreases in myocardial oxygen extraction are related to increases in the carboxyhemoglobin saturation levels. It was observed that some patients evidently could compensate by increasing their coronary blood flows adequately to supply the myocardial tissue with sufficient oxygen, as indicated by a rise in myocardial oxygen uptake in these individuals. However, the other patients with coronary heart disease, evidently more severe, could not increase their coronary blood flow rate enough to compensate for the decreased oxygen carried by the blood. This latter group of patients, even though they had increased cardiac output, had less significant increases of coronary blood flow than those noted in the first group of patients. The coronary arterial-venous oxygen differences and the myocardial tissue oxygen uptakes both decreased, indicating that the myocardial tissue oxygen demand was not being met entirely.

The reduction in the amount of oxygen available to the myocardial tissue caused by the absorption of carbon monoxide from tobacco smoke may be especially critical in persons with pre-existing coronary heart disease, especially when they cannot significantly increase coronary blood flow to compensate for increased myocardial tissue oxygen demand. The carbon monoxide effect may, in part, contribute to the increased incidence of myocardial infarctions that occur in cigarette smokers. Additional research is need[illegible].

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Exercise and oxygen debt. It should be noted that the subjects were healthy without heart disease. The increased postexercise oxygen debt was observed in subjects using a a bicycle ergometer which increases the oxygen consumption 20 to 25 fold:

(not cited) Chevalier et al. (1963) from 300 to 5,833 cc/min

(64) Krumholz et al. (1964) from 300 to 7,900 cc/min.

Such enormous increase in oxygen consumption is not encountered in ordinary work.

This paragraph implies that since carbon monoxide inhalation increases postexercise oxygen debt and smokers also show the effect, that carbon monoxide is the cause in smokers. Reference (21) Chevalier et al. specifically stated that the pathogenesis is unknown. Their summary is as follows:

> Differences have been found in the cardiopulmonary responses to exercise between young male cigarette smokers and nonsmokers. The present study was undertaken in an attempt to determine the cause of such differences. Since smokers carry a chronically elevated carboxyhemoglobin level (>4%), carbon monoxide was inhaled by nonsmokers to raise their carboxyhemoglobin level to the range seen in a control group of smokers. This maneuver caused the development in nonsmokers of an increased oxygen debt with exercise and a reduced pulmonary diffusing capacity at rest. The changes after carbon monoxide inhalation were similar to those found when comparing smokers to nonsmokers. The pathogenesis of these changes are unknown, but support carbon monoxide as a possible etiologic factor accounting for the less efficient exercise and poorer pulmonary function performance of smokers compared to nonsmokers.

In the articles cited above, there are differences in responses to exercise of smokers and of nonsmokers inhaling carbon monoxide. The latter show slowing of the heart rate and decreased oxygen uptake during the working period; smokers show tachycardia and increased oxygen uptake.

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Studies on In Vitro *Thrombus Formation*

Recent studies have indicated that cigarette smoking may accelerate thrombus formation of human blood *in vitro*. Platelet adhesiveness, as measured by *in vitro* tests, also appears to be increased by cigarette smoking (*1, 33, 71, 87*). Other studies, comparing smokers with nonsmokers, indicate that the platelet survival time of the smokers is shortened (*73*) and the platelet turnover rate is increased (*72*). Studies of animals show there is also an increased tendency for the platelets to adhere to the vascular endothelium.

Platelet adhesiveness is reported to be increased in *in vitro* studies using the Chandler rotating loop (*32, 33, 34*); these studies generally show a consistent acceleration of the rate of thrombus formation. Other *in vitro* tests show changes in thrombus formation and some parameters of coagulation as a result of smoking (*56, 66, 87*). However, problems in experimental design and the multiplicity of tests used, measuring either the same or overlapping portions of the complicated coagulation process with varying results, cause difficulty in evaluating these results (*71*).

The mechanism of changes in characteristics of the platelets in smokers is being investigated, but there are indications that the release of catecholamines, especially epinephrine, caused by the absorption of nicotine during smoking may be intimately involved (*71, 72*). In small doses, epinephrine has been shown to promote thrombus formation and coagulation, but in large doses it inhibits these processes. Changes in the electrical charge of the platelet membrane have also been implicated in increasing platelet adhesiveness (*101*), increasing adherence to the vascular endothelium, and accelerating thrombus formation as measured by the Chandler loop method. Some of the alterations in thrombus formation may be mediated by an interaction with serum-free fatty acids and cholesterol (*70*) but current evidence suggests that inhalation of cigarette smoke acts primarily through other independent factors (*101*). Thus, cigarette smoking may cause an acceleration of the *in vitro* thrombus formation of human blood. It is reasonable to suspect that cigarette smoking, in part by affecting the thrombus-forming process in human blood, may account for some of the excess coronary heart disease deaths that occur in cigarette smokers, especially some of the deaths certified as "acute coronary thrombosis." Further research is necessary before any definite conclusion can be made.

Autopsy Studies

The two most significant pathological studies of the relationship of smoking history to atherosclerotic changes in human coronary arteries have been reported by Auerbach and Strong. Auerbach (*7*) studied 1,372 males for whom a smoking history was available and who had died of causes other than coronary heart disease. He found that the percentage of men with an advanced degree of coronary atherosclerosis was higher among cigarette smokers than among nonsmokers, and that the percentage increased with amount of cigarette smoking. Both among smokers and nonsmokers the percentage of men with advanced coronary atherosclerosis also increased with age. This relationship held up even when the following were excluded: men with a history of diabetes, men who had died of any type of heart disease, and men whose hearts weighed 400 gm. or more. A matched set analysis was also carried out (reincluding some diabetics and heart disease deaths) and again the percentage of men with advanced coronary atherosclerosis was less among nonsmokers than among men who had been current cigarette smokers, and this percentage increased with the amount smoked.

Strong (*89*) in a study of coronary arteries from 645 autopsied males, 20 to 64 years of age, excluded patients with diseases he thought to be associated with smoking (emphysema, lung cancer, etc.), or with coronary heart disease (myocardial infarction, hypertension, diabetes, stroke, etc.). He found that the mean percent of coronary intimal surface occupied by raised atherosclerotic lesions was approximately twice as great in heavy smokers (25+ cigarettes/day), and about one-third greater in light smokers (less than 25/day), than in nonsmokers. Calcified lesions and mean coronary wall thickness measured radiographically were on the average highest in heavy smokers and lowest in nonsmokers. Differences among these smoking categories were generally greatest at younger ages.

These autopsy studies suggest that smoking, in addition to the acute immediate effect associated with the act of smoking, has a chronic effect leading to advanced degrees of atherogenesis. However, these findings may, in part, reflect the differences noted between smokers (*7, 89*), particularly heavy smokers, and nonsmokers in regard to greater obesity, higher dietary fat intake, and higher serum cholesterol levels. Further analyses of autopsy series are needed to determine the independent effects of cigarette smoking on atherogenesis.

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The first group of cited references relate to the acute effects of smoking and do not compare smokers and nonsmokers. Even (72) Mustard and Murphy did not compare smokers and nonsmokers but used the same 7 subjects, all heavy smokers who refrained from smoking for at least three weeks. The interpretation of the results should consider the emotional factors involved in abstaining and resuming smoking which are known to influence platelet adhesiveness. The authors accept this possibility which they could not exclude.

Subjects.—A varied group of seven white male veterans was studied. Their ages (given in Table II) ranged between 35 and 72. Three had sustained myocardial infarctions, two cerebrovascular accidents, and one had had recurrent thrombophlebitis, but there had been no overt episodes of vascular disease in any of the patients for some months before the experiment was done. The seventh subject had chronic bronchitis and emphysema without evidence of vascular disease. All were moderately heavy smokers (at least 20 cigarettes a day), but all agreed to refrain from smoking for three weeks immediately prior to one test as well as during the 10 days during which the test was done. Although we cannot be absolutely certain that none of them lapsed occasionally, we are at least certain that their cigarette consumptions were greatly reduced.

Diet.—A diet of uniform composition and caloric content was maintained throughout. The weight of each subject was maintained constant to within 2 lb. (0.9 kg.). The diets had the following composition: fat 22% of calories, protein 15%, carbohydrate 63%. The diets contained no dairy fat or egg yolk except for 7 oz. (200 ml.) of skim milk daily; 30% of the fat was derived from vegetable sources.

Experimental Design.—This was a simple crossover design, three of the subjects selected at random being studied during the non-smoking period first and the smoking period second, and the remaining four in the reverse order. Since the same subjects were studied in the two periods no problem of comparability arises, and comparisons can be made by pairing the results.

These considerations by no means exhaust the possibilities about the means by which smoking influences platelet survival. For example, psychomotor activity is one of the factors which we have not been able to control. We have no evidence bearing on this or on what effect (if any) this may have on platelet economy.

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Smoking and Atherosclerosis. The Letter to the Editor by Burch and Rowell (Br Med J, 23 April, 1966) would be pertinent to examine, relevant to the association between atherosclerosis and smoking.

Smoking and Atherosclerosis

SIR,—You discuss in your leader (26 March, p. 755) the positive association between cigarette smoking and cardiovascular disease. We shall suggest that this is a particular example of a widespread phenomenon.

The sex- and age-distributions[1] of various categories of cardiovascular disease (International Abridged List, 1955: A85, B22–B25, B26—arteriosclerotic and degenerative heart disease—B27, B28, and B29) are all consistent with the view[1,2] that these several diseases have a disturbed-tolerance autoimmune aetiology. This interpretation is supported by the obliterative vascular changes that are observed in kidney homotransplants and which have been attributed to a host-versus-graft reaction.[3] According to the autoimmune theory the cardiovascular disease process is initiated by a small number (generally less than 10) of somatic gene mutations in lymphoid stem cells.[4-6] These spontaneous gene changes initiate the growth of one or more forbidden-clones[6,7] of cells that synthesize autoantibodies. When the target tissue lies behind a blood-tissue barrier the primary autoantibodies are necessarily humoral, and it appears[1,8] that they generally migrate on electrophoresis with the α_2-globulin serum protein fraction. When the target tissue is normally freely infiltrated by small lymphocytes these cells carrying cell-bound autoantibodies act as the primary pathogenic agents. Given this approach, disturbances in the β- and γ-globulin fractions do not represent the primary cause of spontaneous (as opposed to experimental) autoimmune disease but the body's complex response to it.[1,8]

Between the initiation of a forbidden-clone and the first manifestation of symptoms or signs a latent period inevitably intervenes. When the primary autoantibodies are cell-bound (lymphocytic), then on the average this interval, for a given environment, is about twice as long in females as in males; but when the target tissue lies behind a blood-tissue barrier the average latent period is usually of about equal duration in the two sexes.[4,5] From the clinical evidence we deduce[4,5,9] that the length of the latent period is determined in part by the operation of an intrinsic defence mechanism, which in the case of lymphocytic autoimmunity at least is mediated through immunoglobulins. Forbidden-clones are "foreign" and autoantigenic, and they elicit a classical immune response that restrains their proliferation. Probably all disturbed-tolerance autoimmune diseases can be precipitated and exacerbated by extrinsic factors such as certain infective agents and certain drugs.[1,8] Mental stress produces similar effects.[1,8] We have proposed that these several factors either compete for or affect the level of the defence against forbidden-clones.[1,8] Smoking probably acts in the same way. Anticenic and not-self materials entering the body have to be opsonized and phagocytized, and they therefore compete for the finite defence resources. Consequently, the efficiency of the defence against autoantigenic forbidden-clones is diminished. Autoantibodies increase in number, and the latent or chronic autoimmune condition is precipitated or exacerbated.

The idea that the intrinsic defence mechanism in autoimmunity is vulnerable to various extrinsic factors also accounts for the urban-rural differences that are found in connexion with many chronic conditions: the greater pollution of the urban atmosphere and the greater stress of urban life encourage the growth of forbidden-clones. In our view the effect of cigarette-smoking on cardiovascular disease processes is more appropriately described as exacerbating rather than causal.—We are, etc.,

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SMOKING AND CEREBROVASCULAR DISEASE

An increasing amount of evidence has accumulated in the past few years relating the development of clinical cerebrovascular disease to cigarette smoking. Most of this information has come from the prospective mortality studies.

Hammond has reported the following data from his large prospective study (47), noted in table 15.

TABLE 15.—*Cerebral vascular lesions. Age-standardized death rates, by type of smoking (lifetime history) and age at start of study*

	Age			
	45-54	55-64	65-74	75-84
	CVL death rates per 100,000 person-years			
MEN				
Never smoked regularly	28	92	349	1,358
Pipe, cigar	25	100	369	1,371
Cigarette and other	28	129	361	990
Cigarette only	42	130	477	1,165
Total	35	116	391	1,272
WOMEN				
Never smoked regularly	18	57	229	1,032
Cigarette	38	88	315	1,277
Total	25	64	238	1,091
	CVL mortality ratios			
MEN				
Never smoked regularly	1.00	1.00	1.00	1.00
Pipe, cigar	.89	1.09	1.06	1.01
Cigarette and other	1.00	1.40	1.03	.73
Cigarette only	1.50	1.41	1.37	.86
WOMEN				
Never smoked regularly	1.00	1.00	1.00	1.00
Cigarette	2.11	1.54	1.38	1.18

SOURCE: E. C. Hammond (47).

Between the ages of 45 and 74 the death rates from stroke for male smokers were 37 to 50 percent higher than those for male nonsmokers of comparable age. In female smokers the death rates from stroke were 38 to 111 percent greater than those for nonsmokers. Above the age of 74 the differences between the two groups were much less.

The data in Table 16 concerning smoking and death rates from stroke are derived from the U.S. veterans study (52).

TABLE 16.—*Mortality ratios and death rates for stroke as underlying cause among current smokers of cigarettes only*

	Quantity of cigarettes smoked per day				
	0	1-9	10-20	21-39	40+
Mortality ratio (all ages)	1.00	1.51	1.42	1.70	1.59
Death rates:					
Age 55 to 64	59	92	112	125	130
Age 65 to 74	280	323	312	382	502

SOURCE: U.S. veterans study (52).

When stroke was certified as the principal cause of death, the death rates for smokers were higher than for nonsmokers; however, no pronounced increase was noted in the mortality ratios as the degree of smoking increased. The death rates from stroke for all ages was 59 percent higher in heavy smokers (40 or more cigarettes) than in nonsmokers.

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TABLE 17.—*Mortality ratios and death rates for stroke as the underlying or contributory diagnosis among current smokers of cigarettes only*

	Quantity of cigarettes smoked per day				
	0	1-9	10-20	21-39	40+
Mortality ratio (all ages)	1.00	1.45	1.45	1.75	1.83
Death rates:					
Age 55 to 64	101	152	174	195	2 6
Age 65 to 74	424	514	520	616	724

Source: U.S. veterans study (55).

Stroke, listed as either the underlying or contributory cause of death on the death certificate, was also associated with progressively increasing mortality ratios and death rates as the extent of smoking increased. Heavy smokers here had an 83 percent greater mortality from stroke than nonsmokers.

Mortality data by underlying cause of death may often be misleading, particularly when stroke is concerned. Many stroke patients have concomitant coronary heart disease, or may develop pneumonia and other complications that may hasten death. The death certificate may carry stroke as the underlying cause or as the contributory cause of death, depending upon the interpretation of the physician at the time. The important addition of these data is that smoking is associated with a higher mortality from stroke, whether the stroke is recorded as either the underlying cause or as the contributory cause of death.

These two studies indicate that smoking may be associated with a higher mortality from stroke in the relatively younger age groups (under age 74). More than one-half the strokes that occur each year are in the group above age 75 and in this group there is no evidence relating smoking to cerebrovascular disease.

Another large study has been conducted analyzing the mortality of 50,000 former students who entered Harvard University or the University of Pennsylvania during the years 1916–50 (*74, 75, 76*). From this population 171 deaths from cerebrovascular accidents have been identified. A review of the medical records from their college years has been carried out, and selected factors were correlated with the later occurrence of stroke. Seven precursive "risk factors" present at the time of college attendance have been defined: Cigarette smoking, high blood pressure, excess body weight, short stature, a history of early parental death, a history of nonparticipation in college sports, and a history of "heart consciousness" (also shown to be correlated with coronary heart disease). Cigarette smoking and a history of early parental death were more strongly correlated with thrombotic stroke than with hemorrhagic stroke. Students who smoked more than 10 cigarettes daily were at twice the risk of having a fatal stroke than were those who smoked less or not at all.

In 1965 the Framingham study (*54*) reported that while an excess development of thrombotic brain infarction appeared to be associated with cigarette smoking, statistically significant differences could not be demonstrated with the small number of cases available at that time. More recent data from Framingham indicates that cigarette smoking increases the risk of stroke in males. The relatively small number of women smokers had too few strokes for adequate analysis.

The new epidemiological evidence, then, indicates that cigarette smoking may be more closely associated with cerebrovascular disease in the population between the ages of 45 and 74 years than was previously indicated. If cerebrovascular thrombosis (thrombotic brain infarction) accounts for this association, it is possible that some of the considerations of how cigarette smoking may produce coronary thrombosis also apply to the pathogenesis of cerebrovascular disease. Further research is essential to understand the relationships that exist between cigarette smoking and cerebrovascular disease.

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Additional information on mortality data concerning aortic aneurysm has been provided by the U.S. veterans study (52) and the Hammond (47) studies, as noted in tables 18 and 19, respectively.

TABLE 18.—*Mortality ratios and age-standardized death rates for aortic aneurysm in U.S. veterans, current smokers of cigarettes only*

	Number of cigarettes smoked per day				
	0	1-9	10-20	21-39	40+
Mortality ratio	1.00	2.12	5.53	5.95	7.28
DEATH RATES					
Age:					
55 to 64	6	13	27	43	44
65 to 74	25	57	123	157	221

Source: U.S. veterans study (52).

TABLE 19.—*Mortality ratios and age-standardized death rates for aortic aneurysm*

	Age 45-64 years		Age 65-79 years	
	Females	Males	Females	Males
Mortality ratio	3.89	2.62	3.33	4.92
Death rates	[1] 4(1)	18(7)	43(15)	118(24)

[1] Numbers in parentheses indicate death rates of those who never smoked regularly.

Source: Hammond, E. C. (47).

It is apparent that there is a close association between cigarette smoking and death caused by aortic aneurysms.

Thus, the additional evidence confirms the previously observed association between cigarette smoking and death due to nonsyphilitic aortic aneurysm.

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The Health Consequences of SMOKING

1968 SUPPLEMENT TO THE
1967 Public Health Service Review

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service

CHAPTER 1

Smoking and Cardiovascular Diseases

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INTRODUCTION

The primary purpose of the 1968 Supplemental Report is to review the pertinent literature that has become available subsequent to the 1967 Report. Brief mention of the conclusions of the 1964 Report and the highlights of the 1967 Report is made to facilitate an understanding of the significance of the most recent information. The current research findings should be considered in the perspective of the research evidence previously presented in the 1964 (*148*) and 1967 (*146*) Reports.

Conclusions of the 1964 Report (*148*)

Male cigarette smokers have a higher death rate from coronary artery disease than nonsmoking males, but it is not clear that the association has causal significance.

Highlights of the 1967 Report (*146*)

1. Additional evidence not only confirms the fact that cigarette smokers have increased death rates from coronary heart disease, but also suggests how these deaths may be caused by cigarette smoking. There is an increasing convergence of many types of evidence concerning cigarette smoking and coronary heart disease which strongly suggests that cigarette smoking can cause death from coronary heart disease.

2. Cigarette smoking males have a higher coronary heart disease death rate than nonsmoking males. This death rate may, on the average, be 70 percent greater, and in some, even 200 percent greater or more in the presence of other known "risk factors" for coronary heart disease. Female cigarette smokers also have a higher coronary heart disease death rate than do nonsmoking females, although not as high as that for males. In general, the death rates from this disease increase with amount smoked. Cessation* of cigarette smoking is followed by a reduction in the risk of dying from coronary heart disease when compared with the risk incurred by those who continue to smoke.

3. A greater frequency of advanced coronary arteriosclerosis is noted in male cigarette smokers, especially in those who smoke heavily.

4. Additional evidence strengthens the association between cigarette smoking and cerebrovascular disease, and suggests that some of the pathogenetic considerations pertinent to coronary heart disease may also apply to cerebrovascular disease.

*Those who have stopped smoking cigarettes have a lower risk of dying from coronary heart disease than those who continue to smoke.

SMOKING AND CORONARY HEART DISEASE

Coronary Heart Disease Mortality

As in the past two decades, coronary heart disease in the United States continues as the leading cause of death, being responsible in 1967 for 567,710 deaths or 31.0 percent of the total of 1,833,900 deaths.

Since age specific data are not yet available for 1967, table 1 shows the number of deaths due to coronary heart disease and the death rates per 100,000 persons by age for 1966.

Table 1.—*Coronary heart disease deaths and death rates per 100,000 population, by age: United States, 1966*

[Disease category 420 in the ICD Manual, 1955]

Age	Number of deaths	Death rates
Total	573,191	292.7
Under 25 years	250	0.3
25–34 years	1,469	6.6
35–44 years	12,522	52.0
45–54 years	45,997	206.3
55–64 years	99,647	577.3
65–74 years	162,555	1,405.2
75–84 years	171,737	2,979.5
85 and over	78,854	7,015.5
Not stated	160	(X)

X—Not applicable.

Source: Monthly Vital Statistics, National Center for Health Statistics (147).

These data illustrate the dramatic increase in death rates as age advances, with the increase being particularly marked after age 15. The death rates for coronary heart disease for men and women continue to show a conspicuous difference. In 1966 it was 361.6 for males and 226.5 for females per 100,000 population.

(148) U.S. Public Health Service. Smoking and Health. Report of the Advisory Committee to the Surgeon General of the Public Health Service, Washington, U.S. Department of Health, Education, and Welfare, Public Health Service Publication No. 1103, 1964. 387 pp.

(146) U.S. Public Health Service. The Health Consequences of Smoking. A Public Health Service Review: 1967. Washington, U.S. Department of Health, Education and Welfare, Public Health Service Publication No. 1696, 1967. 227 pp.

(147) U.S. Public Health Service. National Center for Health Statistics. Monthly Vital Statistic Report. Final Mortality Statistics 16(2) (Supplement): 1–12, March 12, 1968.

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While several studies of various aspects of the association between coronary heart disease mortality and cigarette smoking have been reported during the past year, the most significant studies of this association are contained in the 1967 report.

The several new studies of various aspects of the association between coronary heart disease mortality and cigarette smoking follow.

Friedman (*46*) reported a strong positive correlation between per capita cigarette sales and coronary heart disease death rates by states. The correlation is 0.76 when data only from those states with relatively accurate information of cigarette consumption are analyzed. Related factors such as urbanization or softness of the local water supply do not explain this degree of association.

Other studies deal with the excess deaths associated with smoking. Strobel, et al. (*149*) reported that among 3,479 Swiss physicians, over 50 percent of the excess deaths occurring over a 9-year period among smokers was due to coronary heart disease.

In contrast to the study above and data from the United States in which approximately one-half of the excess deaths associated with smoking are attributed to cardiovascular causes (*143*), preliminary data from Hirayama (*65*) show that the excess deaths in Japan associated with smoking were primarily explained by cancer of various sites. Only 12 percent of the excess deaths were associated with cardiovascular causes. This prospective study of 265,118 adults over the age of 40 encompassed a followup period of 15 months. Additional follow-up by Hirayama should yield useful data with respect to smoking and excess mortality from cardiovascular diseases in this Japanese population group, particularly with regard to the younger adults in the study.

Hyams, et al. (*67*), on the other hand, speculate that the apparent increase in the occurrence of coronary heart disease among Japanese males, especially under the age of fifty, may be due to a trend toward Westernization in both diet and smoking habits among younger Japanese men.

Hammond (*54*), in his prospective study of over 1 million men and women, showed a positive relationship between the duration of the smoking habit and coronary heart disease mortality. In the Framingham Heart Study (*71*), no association was found between the duration of the smoking habit and the incidence of mortality from heart attacks among men who were "heavy smokers" (more than one package of cigarettes per day).

These discrepancies between the relationship of smoking to the incidence of total coronary heart disease and mortality from acute coronary heart disease may be accounted for, in part, by the differences in population groups studied and by the possibility that duration of smoking may have a greater association with the fatal forms of coronary heart disease.

Kannel, et al. (*70*), in more recent data from the Framingham study, indicate that the fatal and more severe forms of coronary disease are more strongly associated with cigarette smoking that the less severe forms (figure 1).

(46) Friedman, G. D. Cigarette smoking and geographic variation in coronary heart disease mortality in the United States. Journal of Chronic Diseases 20: 769-779. 1967.

(149) Strobel, M., Gsell, O. Mortalität in Beziehung zum Tabakrauchen: 9 Jahre Beobachtungen bei Ärzten in der Schweiz. Helvetica Medica Acta 32(6): 547-593. December 1965.

(65) Hirayama, T. Smoking in relation to the death rates of 265,118 men and women in Japan. Tokyo, National Cancer Center Research Institute, September 1967. 14 pp.

(67) Hyams, L., Seel, M., Archer, M. Myocardial infarction in the Japanese. A retrospective study. American Journal of Cardiology 20(4): 548-554. October 1967.

(54) Hammond, E. C. Smoking in relation to the death rates of 1 million men and women. In: Haenszel, W., editor. Epidemiological Approaches to the Study of Cancer and Other Diseases. Bethesda, U.S. Public Health Service, National Cancer Institute Monograph No. 19. January 1966. Pp. 127-204.

(71) Kannel, W. B., Dawber, T. R., McNamara, P. M. Detection of the coronary-prone adult: The Framingham Study. Journal of the Iowa Medical Society 56(1): 26-34. January 1966.

(70) Kannel, W. B., Castelli, W. P., McNamara, P. M. The coronary profile: 12-year follow-up in the Framingham study. Journal of Occupational Medicine 9(12): 611-619. December 1967.

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Coronary Heart Disease Morbidity *

Much of the morbidity data reported during this past year resulted from retrospective studies of patients or cross-sectional studies (*106, 107, 127, 131, 151*). In these studies the findings revealed that there

* Also may include mortality data in this presentation.

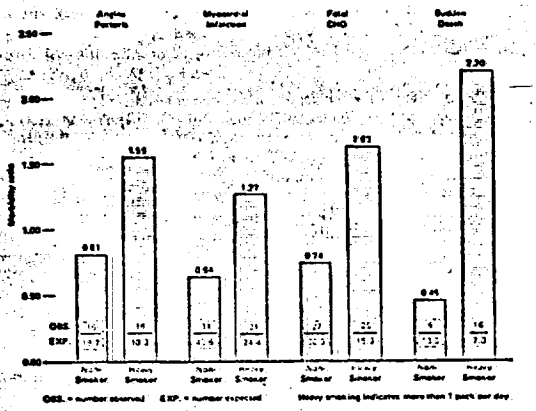

FIGURE 1—Morbidity ratios for specified manifestations of coronary heart disease, among men aged 50–59 years at entry into Framingham Heart Study, classified by smoking habit: 12 years' experience.

SOURCE: Kannel, et al. (70).

were relatively more smokers among the groups with coronary heart disease, than among the comparison, or control groups.

In a retrospective study of myocardial infarction patients in Japan, Hyams, et al. (67) reported similar findings, particularly among the men under age 50. Differences measured by an exposure index combining intensity and duration of smoking showed the same trend, though the data were not statistically significant.

Dorken (*30, 31*) reported on two retrospective studies in Hamburg, Germany: one, a study of female patients; the other, a study of male patients. He concluded that there is a strong association between smoking and myocardial infarction in both males and females under the age of 45.

In Dublin, Mulcahy, et al. (*106, 108, 109*) studied groups of male and female coronary heart disease patients under age 60. He found that a much greater portion of the patients, in comparison with a sample of the general population, smoked cigarettes. Also, the intensity (amount multiplied by duration) of smoking was as much as 2½ times greater among the male patients and 3 times greater among the female coronary heart disease patients as contrasted with the males and females in the general population.

In a study of 675 aviators, smoking histories taken in 1963 did not show a positive association in the prevalence of coronary heart disease with either amount, duration, or intensity of smoking. These findings are based on 38 cases (5.7 percent) of coronary heart disease of all forms among a very select population and are therefore subject to large sampling variations (*96*). Moreover, since smokers may have an excessive mortality during an acute myocardial infarction, as mentioned before, prevalence rates are not as good a measure of the association between smoking and coronary heart disease as are incidence rates.

Epstein (*39*), although finding no prevalence differences between smokers and nonsmokers in his Tecumseh Study, found an increased incidence in cigarette smokers of both fatal and nonfatal coronary heart disease.

In a short prospective study of 11,000 Norwegian men (12,000 with smoking histories), Natvig (*113*) did find an increased risk of incidence of first myocardial infarction or angina pectoris among those men 50–59 years of age who smoked.

Since the 1967 Report, the continuing prospective epidemiologic studies leave somewhat clarified the differential relationship between smoking and each of the manifestation categories of coronary heart disease: angina, nonfatal myocardial infarction, fatal myocardial infarction and sudden death.

(106) MULCAHY, R., HICKEY, N. J. Cigarette smoking habits of patients with coronary heart disease. British Heart Journal 29: 404–408, 1966.

(107) MULCAHY, R., HICKEY, N. J. The role of cigarette smoking in the causation of atherosclerosis. Geriatrics 22(2): 165–174, February 1967.

(127) ROTH, O., ERNST, A., WOLFF, G. D. Long range observations in fifty thirty young patients with myocardial infarction. American Journal of Cardiology 19(3): 331–338, March 1967.

(131) SILVERS, M. I. Myocardial infarction among southwestern American Indians. Annals of Internal Medicine 67(4): 836–847, October 1967.

(151) VELLIGER, U., HEYDEN-STUCKY, S. Das Infarktprofil. Unterschiede zwischen Infarktpatienten und Kontrollpersonen in der Ostschweiz. Schweizerische Medizinische Wochenschrift 96(23): 748–758, June 11, 1966.

(30) DÖRKEN, H. Die Rauchgewohnheiten bei Jüngeren Frauen mit Herzinfarkt. Münchener Medizinische Wochenschrift 109(41): 2129–2134, January 1967.

(31) DÖRKEN, H. Die Rauchgewohnheiten bei Jüngeren Herzinfarkt-Patienten. Münchener Medizinische Wochenschrift 109(4): 187–192, January 27, 1967.

(108) MULCAHY, R., HICKEY, N. J., MAHER, B. J. The aetiology of coronary heart disease in women. Journal of the Irish Medical Association 60 (335): 23–29, January 1967.

(109) MULCAHY, R., HICKEY, N. J., MAHER, B. J. Coronary heart disease in women. Study of risk factors in 100 patients less than 60 years of age. Circulation 36(4): 577–586, April 1967.

(96) LANE, N. E., ORLEBAR, A. The thousand aviator study: Smoking history correlates of selected physiological, biochemical, and anthropometric measures. U.S. Naval Aerospace Medical Institute, NAMI-951. Under the Joint sponsorship of the U.S. Public Health Service, and the National Aeronautics and Space Administration, NASA Order R-130, April 27, 1966. 12 pp.

(39) EPSTEIN, F. H. Some uses of prospective observations in the Tecumseh Community Health Study. Proceedings of the Royal Society of Medicine 60(1): 4–8, January 1967.

(113) NATVIG, H. Effekten av umettede fettsyrer på hyppigheten av hjerteinfarkt M.H. Resultatet av befolkningsundersøkelsen "Oslo-forsøk." Tidsskrift for den Norske Laegeforening 87(11): 1033–1041, June 1967.

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Data from the Framingham Heart Study (*69*) revealed that "heavy" cigarette smoking, more than 20 cigarettes per day, is positively associated with uncomplicated angina in males but not in females (figure 2).

Similar findings were reported by Weinblatt (*155*) in a study of male subjects in the Health Insurance Plan with the associations more pronounced among those men who smoked two or more packages of cigarettes per day. As can be seen, in table 2, the arithmetic differences in rates between smokers and nonsmokers are greater for myocardial infarction than for angina; however, the risk ratios are similar.

In a retrospective study, Heyden-Stucki et al. (*61*) found no association of smoking with angina or other chest complaints.

The inconsistencies in data on the association between smoking and the development of angina may be due in part to differences in methods used to diagnose and classify angina and to record smoking habits in these epidemiologic studies. Further standardization in this area may help to determine more accurately the relationship of smoking to angina.

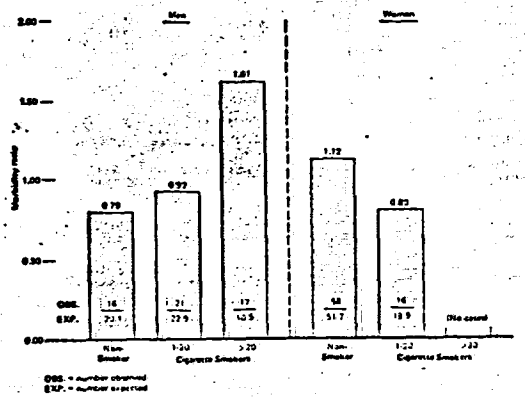

FIGURE 2—Angina pectoris morbidity ratios among persons aged 30–59 years at entry into Framingham Heart Study, classified by sex and number of cigarettes smoked: 12 years' experience.

SOURCE: Kannel, et al. (*69*).

TABLE 2.—*Age-adjusted incidence rates per 1,000 males aged 35–64, and morbidity ratios, for specified manifestations of coronary heart disease, by smoking category: Health Insurance Plan Study*

[5 year observation data]

Smoking category	Myocardial infarction		Angina	
	Incidence rate	Morbidity ratio	Incidence rate	Morbidity ratio
Current nonsmokers	3.27	1.0	1.37	1.0
Current cigarette smokers	7.01	2.1	2.62	1.9
Less than 2 packs	5.05	1.5	2.03	1.5
2 or more packs	20.80	6.4	6.64	4.8

SOURCE: Weinblatt, E. (*155*).

In the Western Collaborative Study, Rosenman et al. reported higher rates of silent myocardial infarctions in younger men, and higher rates of recurrent myocardial infarctions at all ages among those who smoked more than 25 cigarettes per day (*123, 124*).

Friedemann, et al. (*44*) reported reinfarctions occurred more frequently among smokers than nonsmokers.

Dorken (*29*) found in a series of 550 men of all ages, in Hamburg, who survived at least 5 and up to 6 years after their first myocardial infarction, that 172 (52 percent) had stopped smoking completely after the first infarction. In contrast, of 55 subjects who had died from a second myocardial infarction or sudden coronary death after leaving the hospital, only 25 (42.9 percent) had given up smoking completely ($P<0.001$).

(69) KANNEL, W. B., CASTELLI, W. P., MCNAMARA, P. M. Cigarette smoking and risk of coronary heart disease. Epidemiologic clues to pathogenesis: The Framingham Study. In: Wynder, E. L., Hoffmann, D., editors. Toward A Less Harmful Cigarette. Bethesda, U.S. Public Health Service, National Cancer Institute Monograph 28, June 1968. (In press)

(155) WEINBLATT, E. Personal communication. April 1968.

(61) HEYDEN-STUCKY, S. SCHIELA-REICH, S. Cardiologische Risikofaktoren bei Schweizer Mannern. Schweizerische Medizinische Wochenschrift 97 (1): 20–25, January 7, 1967.

(123) ROSENMAN, R. H., FRIEDMAN, M., JENKINS, C. D., STRAUS, R., WURM, M., KOSITCHEK, R. Clinically unrecognized myocardial infarction in the Western Collaborative Group Study. American Journal of Cardiology 19(6): 776–782, June 1967.

(124) ROSENMAN, R. H., FRIEDMAN, M., JENKINS, C. D., STRAUS, R., WURM, M., KOSITCHEK, R. Recurring and fatal myocardial infarction in the Western Collaborative Group Study. American Journal of Cardiology 19(6): 771–775, June 1967.

(44) FRIEDEMANN, M., STEIN, H., EMMRICH, J., REINERT, H. Der Herzinfarkt in Atiologischer und Katamnestischer Sicht. Deutsches Archiv fur Klinische Medizin 214: 264–280, 1963.

(29) DORKEN, H. The etiology of myocardial infarction—with special reference to cigarette smoking among young coronary patients and those with second heart attacks. In: Wynder, E. L., Hoffmann, D., editors. Toward a Less Harmful Cigarette. Bethesda, U.S. Public Health Service, National Cancer Institute Monograph 28, June 1968. (In press)

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Relationships of Cigarette Smoking to Other Risk Factors

The ongoing prospective and other epidemiologic studies have yielded findings which permit analysis of the interrelationships among cigarette smoking and other factors considered to increase the risk of coronary heart disease.

Age

Generally, the findings show that the incidence rate of coronary heart disease increases with age, both among smokers and nonsmokers. The morbidity ratio of coronary heart disease in smokers versus nonsmokers decreases with age though the absolute number of excess deaths among smokers increases with age.

High Blood Pressure

Recent reports on the relationship between smoking and blood pressure appear to support the findings in the 1967 report:

> Although the inhalation of cigarette smoke is frequently accompanied by acute transient elevations in blood pressure, habitual smokers tend to have lower blood pressures than do nonsmokers. But, given the presence of high blood pressure in an individual, smoking acts as an additional risk factor for the development of coronary heart disease.

Heyden-Stucki et al. (*61*) report that among 500 workers in Switzerland, smokers, particularly heavy smokers, have lower blood pressure as a group than do nonsmokers. Smokers also were found to have normal or subnormal weights in contrast to nonsmokers who had a greater mean weight; thus, confounding the relationship between smoking and blood pressure level. Tibblin (*144*) in a cohort study of Scandinavian men born in 1913, found a lower mean blood pressure among smokers than among nonsmokers. As the population was classified according to levels of blood pressure, a step-wise decrease in the prevalence of smoking was noted as the level of blood pressure increased. A similar trend for both systolic and diastolic pressures was also reported by Clark, et al. (*23*) as shown in table 3.

Table 3.—*Mean age and mean systolic and diastolic blood pressure, by smoking category: Los Angeles Heart Study, 1963*

Current cigarette smoking status			Blood pressure (mm. of Hg.)	
	Number of subjects	Years of age	Systolic	Diastolic
Smokers	407	54	133.6	82.5
Nonsmokers	728	57	137.0	83.9

Source: Clark, V. A. (*23*).

In the study of 675 aviators (*96*) smoking intensity, although not found to be associated significantly with systolic or diastolic blood pressures, was positively associated with pulse pressure. Reid, et al. (*122*) in a comparative study of workers in Great Britain and the United States noted lower diastolic blood pressures among smokers than among nonsmokers in both groups; adjustment for weight variations reduced this difference appreciably.

Mulcahy (*107*), in a retrospective study of 100 women coronary heart disease patients under 60 years of age, reported that 50 to 60 percent had diastolic hypertension (>90 mm Hg.). Hypertension and cigarette smoking, together or separately, were present in over 80 percent of these patients.

In the major prospective studies, when both smoking and hypertension were present, an interactive increase in the risk of developing coronary heart disease was noted. When to these two risk factors elevated cholesterol levels were added, the risk of developing coronary heart disease was further increased (figures 3 and 4).

(144) Tibblin, G. High blood pressure in men aged 50—A population study of men born in 1913. Acta Medica Scandinavica (Supplementum 470): 1–81, 1967.

(23) Clark, V. A., Chapman, J. M., Coulson, A. H. Effects of various factors on systolic and diastolic blood pressure in the Los Angeles Heart Study. Journal of Chronic Diseases 20: 571–581, 1967.

(122) Reid, D. D., Holland, W. W., Rose, G. A. An Anglo-American cardiovascular comparison. Lancet 4(7531): 1375–1378, December 30, 1967.

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Hypertension and Smoking. The article by (107) Mulcahy does not contain any information on hypertension. There are 77 women reported to have coronary heart disease and their smoking habits were matched with statistics of the general female population. The relevant paragraph and Table are as follows:

Table 2 illustrates the smoking experience of the 77 female patients with classical CHD under 60 years who were seen by us. The numbers are small and further study is clearly needed, but already we can identify a significant deficiency of nonsmokers and ex-smokers among our female patients compared

Table 2 Ratio of smokers to nonsmokers in 77 female patients under 60 years with CHD compared to estimated ratio in general female population for age group 35 to 59 in 1961

Category	Present enquiry		Female population* (age group 35-59)	
	No. of patients	%	No. of subjects	%
Smokers	49	64	261	45.6
Ex-smokers	1	1	52	9.1
Nonsmokers	27	35	259	45.3
Total	77	100	572	100

Significant at the 1% level

*Source: "Statistics of Smoking in the Irish Republic," Research Services, Limited, Dublin, 1962

to the general female population. Also, our 77 patients are on average more than 2½ times heavier smokers than the general Irish female population of the same age group.

Our finding of a significant association between cigarette smoking and CHD in women confirms the findings of M. F. Oliver of Edinburgh[4] who noted an excess of smokers and a deficiency of nonsmokers and ex-smokers among 50 women less than 45 years of age with cardiac infarction. He found little or no connection between cigarette smoking and angina pectoris among young women. Our 23 females with angina pectoris had a lighter smoking experience than the 54 with cardiac infarction or acute coronary insufficiency, but nevertheless they had a heavier experience than the general population.

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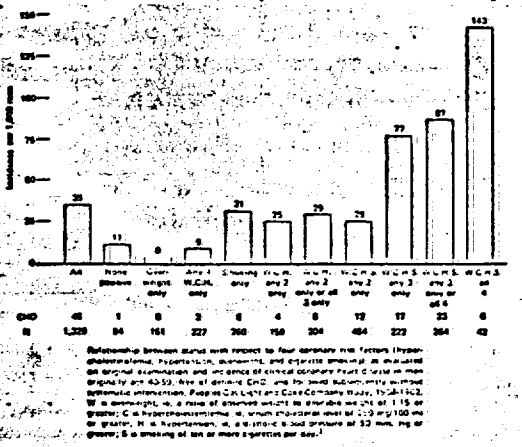
Certain of the retrospective and cross-sectional studies (*62, 151*) have, in general, demonstrated higher cholesterol levels in smokers than in nonsmokers. Pincherle, et al. (*119*) and Lane, et al. (*96*) report similar findings. A study by Heyden-Stucki (*61*) of 500 Swiss workers found a similar trend but the differences between smokers and nonsmokers with respect to cholesterol levels and other lipids were not statistically significant.

A recent report (*36*) describes some of the variability of interrelationships among smoking, blood pressure and cholesterol levels in different population groups throughout the world. It concludes that though nonsmokers tend to be heavier and have higher blood pressure levels than cigarette smokers, heavy smokers tend to be in the top



Relationship between status with respect to four coronary risk factors (hypercholesterolemia, hypertension, overweight, and cigarette smoking) as evaluated on original examination and incidence of clinical coronary heart disease in men originally age 40-59, free of definite CHD, and followed subsequently without systematic intervention. Peoples Gas Light and Coke Company Study, 1958-1962. W is overweight, i.e., a ratio of observed weight to desirable weight of 1.15 or greater; C is hypercholesterolemia, i.e., serum cholesterol level of 250 mg/100 ml or greater; H is hypertension, i.e., a diastolic blood pressure of 90 mm. Hg or greater; S is smoking of ten or more cigarettes per day.[1]

FIGURE 3—Incidence of coronary heart disease among men aged 40–59 years at entry into Peoples Gas Light and Coke Company Study, classified as to presence of specified risk factors: 1958–1962.

SOURCE: Stamler, et al. (*138*).

deciles for blood pressure and relative weight. Cholesterol-smoking relationships described in these studies do not show a consistent pattern.

In a controlled dietary intervention study of postinfarction patients Leren (*97*) found that smoking habits did not influence the serum cholesterol level or the coronary heart disease relapse rate in the control group. Among the study group of dieters there was a suggestion, although not statistically significant at the 0.05 level, that smokers had a higher coronary heart disease relapse rate than nonsmokers.

(*62*) HEYDEN-STUCKY, S. Epidemiologie des Herzinfarktes 1965. Schweizerische Medizinische Wochenschrift 95(45): 1535–1540, November 6, 1965.

(*119*) PINCHERLE, G., WRIGHT, H. B. Screening in the early diagnosis and prevention of cardiovascular disease. Journal of the College of General Practitioners 13: 280–289, 1967.

(*36*) Epidemiological studies related to coronary heart disease: Characteristics of men aged 40–59 in seven countries. F. Smoking habits. Acta Medica Scandinavica (Supplement 460): 304–315, 1967.

(*138*) STAMLER, J., BERKSON, D. M., LEVINSON, M., LINDBERG, H. A., MOJONNIER, L., MILLER, W. A., HALL, Y., ANDELMAN, S. L. Coronary artery disease. Status of preventive efforts. Archives of Environmental Health 13(3): 322–335, September 1966.

(*97*) LEREN, P. The effect of plasma cholesterol lowering diet in male survivors of myocardial infarction. A controlled clinical trial. Acta Medica Scandinavica (Supplement 466): 1–92, 1966.

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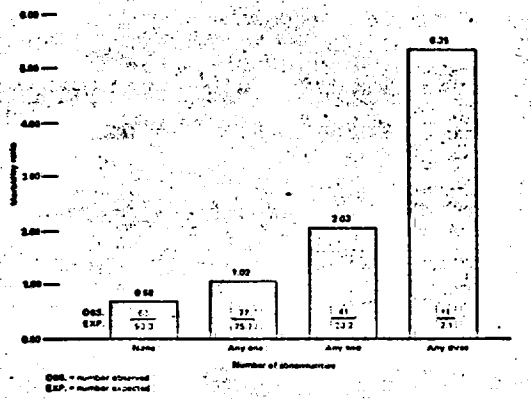
Physical Inactivity

The independent and combined effects of cigarette smoking and physical activity, as described in the 1967 report, continue to be demonstrated as more data are accumulated. The apparent protective effect of physical activity appears to be more pronounced with regard to myocardial infarction than angina [table 4, (155)]. Differences in methods of assessment of history of physical activity in case versus



OBS. = number observed
EXP. = number expected

FIGURE 4—Myocardial infarction morbidity ratios among men aged 30–59 years at entry into Framingham Heart Study, classified according to presence of selected risk factors: 12 years experience (Risk factors are: cholesterol level over 250 mg/100 ml., systolic blood pressure over 160 mm. Hg., smoking over 1 pack of cigarettes per day).

SOURCE: Kannel, et al. (70).

control groups may account for some differences in the incidence rates noted.

Blackburn, et al. (10) found no relationship of smoking to the prevalence of postexercise ECG changes in a study of 10,200 men age 40 to 59 years. However, there were only 510 (5.1 percent) subjects with a "positive" ECG response.

Sociological, Psychological and Personality Variables

Two studies (35, 64) demonstrated an inverse relationship between the frequency of coronary heart disease and the educational level of the subjects. In the Bell Telephone System (64), those men without a college education had higher coronary heart disease rates than those with a college education. Also, those not attending college tended to smoke more.

In a study of factors related to coronary heart disease among Cleveland attorneys (35), the quality of the law schools attended by the sub-

TABLE 4.—*Annual age-adjusted incidence rates of specified manifestations of coronary heart disease per 1,000 males aged 35–64 and corresponding morbidity ratios, by smoking habits and physical activity class: Health Insurance Plan Study*

[8 year observation data]

Smoking status and physical activity class	Myocardial infarction		Angina	
	Incidence rate	Morbidity ratio	Incidence rate	Morbidity ratio
All current nonsmokers	3.27	1.0	1.37	1.0
Not cigarette smokers:				
Least active	6.33	1.9	2.14	1.6
Intermediate	3.07	0.9	1.67	1.2
Most active	3.01	0.9	1.32	1.0
All current cigarette smokers:				
Least active	10.59	3.3	2.31	1.7
Intermediate	5.50	1.8	2.93	2.1
Most active	5.77	1.8	2.74	2.0
Less than 2 packs:				
Least active	7.61	2.3	2.05	1.5
Intermediate	4.71	1.4	2.37	1.7
Most active	3.85	1.2	1.93	1.4
2 or more packs:				
Least active	39.09	12.0	4.97	3.6
Intermediate	11.27	3.5	5.09	3.7
Most active	24.09	7.4	12.29	8.9

(10) BLACKBURN, H., KEYS, A., KARVONEN, M., VAN BUCHEM, F. S. P., TAYLOR, H. L. Relation of "positive" postexercise electrocardiographic responses to other characteristics of risk. Circulation 36(4) (Supplement II): 70. October 1967.

(35) FRIEDMAN, E. H., HELLERSTEIN, H. K. Occupational stress, law school hierarchy, and coronary artery disease in Cleveland attorneys. Psychosomatic Medicine 29(1): 72–86, January–February 1967.

(64) HINKLE, L. E., JR., WHITNEY, L. H., LEHMAN, E. W., DUNN, J., BENJAMIN, B., KING, R., PLAKUN, A., FLEHINGER, B. Personal Communication, 1968.

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Postexercise ECG Changes. The observations of (10) Blackburn et al. are very important because they relate to the incidence of myocardial ischemia in 10, 260 men. That 519 subjects had positive ECG response should not deter from the significance of the investigation. The reference is actually an abstract which is not normally cited as a primary source of information. Hower the 1968 document is full of abstracts and personal communications.

Relation of "Positive" Postexercise Electrocardiographic Responses to Other Characteristics of Risk

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The electrocardiographic response to exercise has become a powerful tool for identifying greatly increased risk of acute coronary episodes in otherwise "healthy" individuals. It is now necessary to establish how much it really adds to information over and above already known factors of risk. This was first examined by a study of the interrelations of a "positive" exercise ECG response with other measurable physical characteristics and habits. It is best studied in natural populations which contain realistic proportions of "positive" and "negative" responders and broad ranges of characteristics. Here the frequency of 519 "positive" responses among 10,260 men aged 40 to 59 years was plotted according to increasing obesity, blood pressure, and serum cholesterol, and activity and smoking habits.

The test was a standard three-minute, constant-rate step, and criteria for "positive" tests were rigidly defined. The most important association was a linear relationship between frequency of "positive" ECG responses and level of systolic blood pressure ($P < 0.0001$ between lowest and highest pressure classes). No relation of exercise response to fatness was found through the bulk of the distribution, but among the upper 20% of men ranked by skinfold thickness the rate of "positive" responses was significantly greater ($P < 0.001$ between lowest and highest obesity classes). There was a decreasing rate of "positives" with increasing physical activity class and no relationship to serum cholesterol or smoking habit. Evaluation of the prognostic power of the exercise ECG requires, at the least, consideration of age, sex, blood pressure, and obesity.

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ject were ranked independently by a law school professor. Lawyers attending schools in the "highest law school quality group" had lower rates of coronary heart disease than those attending schools in the "lower law school quality group." Also, those in the latter group had started smoking at an earlier age. Since additional differences were noted for other risk factors, smoking alone may not be responsible for the total differences in these rates. In both studies, it was hypothesized that with respect to susceptibility to development of coronary heart disease, behavior patterns and attitudes established prior to professional training and prior to stresses resulting from job mobility and job tension, were more significant than the later stresses which resulted from their present jobs.

Recent data from the Western Collaborative Group Study (*125*) appear to show that among men 39–49 years of age, cigarette smoking was associated with several coronary heart disease risk factors (table 5). Though these findings may be statistically significant, the differences between smokers and nonsmokers were small.

(125) Rosenman, R. H., Friedman, M., Jenkins, C. D., Zyzanski, S. J. Personal Communication, 1968.

TABLE 5.—*Age-adjusted means for selected coronary heart disease risk factors and personal characteristics, by smoking category: Western Collaborative Group Study, males 39–49 years of age*

[8½ years average observation data]

Variable	Smoking category		Percent difference
	Never smoked	Smoked 25 cigarettes or more per day	
Serum cholesterol	217.2	231.8	+6.7
Beta/alpha ratio	1.9	2.1	+10.5
Lipalbumin	21.1	19.4	−8.1
Systolic blood pressure	126.3	129.9	+2.9
Diastolic blood pressure	82.0	81.3	−0.9
Ponderal index	12.6	12.7	+0.8
Physical activity on job	1.95	1.95	0
Amount of exercise	2.18	2.05	−6.0
Income	2.75	2.75	0

Source: Rosenman, R. H. (125).

TABLE 6.—*Percent distribution by behavior type of smokers and nonsmokers: Western Collaborative Group Study, males 39–49 years of age*

[8½ years average observation data]

Behavior type	Total	Smoking category					
		Never smoked	Former smokers	Current pipe or cigar only	1–15 cigarettes per day	16–25 cigarettes per day	26 cigarettes or more per day
Total	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Type A	47.5	41.3	45.0	48.3	44.8	48.9	56.7
Type B	52.5	58.7	55.0	51.7	55.2	51.1	43.3

Test of difference of distributions: $X^2 = 26.70$; df = 3; $p = .001$.

Source: Rosenman, R. H. (125).

Behavioral pattern type A is characterized by an enhanced competitiveness, drive, aggressiveness and hostility, and an excessive sense of time urgency as contrasted to type B. There was a difference in the distribution of personality types A and B among smokers and nonsmokers (table 6).

The foregoing data refer to concurrent observations gathered in 1960–1961 on 3,182 men who were then free of manifestations of coronary heart disease. A follow-up of this population during the next 4½ years disclosed that cigarette smokers experienced substantially higher rates of coronary heart disease than those who had never smoked. This finding is based on data for men 39–49 years of age, which have been adjusted for the confounding influences of related risk factors, such as age, cholesterol, etc. (table 7).

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TABLE 7.—*Incidence of new coronary heart disease by smoking category: Western Collaborative Group Study, males 39–49 years of age*

[4½ years average observation data]

Smoking category	Number of men	Rate per 10,000 population	
		Adjusted for concomitant variables	Not adjusted
Never smoked	340	38	29
Former cigarette smokers	241	67	92
Pipe and cigar only	406	27	16
1–15 cigarettes	212	51	52
16–25 cigarettes	436	89	92
26 cigarettes and over	425	93	104

SOURCE: Rosenman, R. H. (115).

The coronary heart disease rate for those men smoking 26 or more cigarettes a day is seen to be about three times greater than for those who never smoked. The rate for former smokers is still rather high, even after adjustment for concomitant variables. The largest impact of the adjustment procedure is noted among this group, and suggests that those who quit may have done so because they were already a relatively high-risk group for reasons other than smoking. The relatively low rate among men smoking only pipes and cigars is noted in this as in other prospective studies.

The nature of the association of smoking and coronary heart disease incidence among type A and type B personality groups is not easy to characterize or interpret. Among the type A group, the pipe and cigar smokers and the light cigarette smokers had the lowest rates of incidence of new coronary heart disease, while the highest rates were found among those smoking 26 or more cigarettes a day. For the type B group, the lowest rates occurred among those who had never smoked, and the highest among the light cigarette smokers. The age-adjusted rates of new incidence of coronary heart disease per 10,000 men 39–49 years of age are shown in table 8.

Additional data to permit concomitant analysis of these variables and those in table 7 are needed.

TABLE 8.—*Incidence of new coronary heart disease by smoking category and behavior type: Western Collaborative Group Study, males 39–49 years of age*

[4½ years average observation data]

Smoking category	Rate per 10,000 population	
	Behavior type A	Behavior type B
Total	91	33
Never smoked	53	13
Former smokers	107	36
Pipe and cigars only	18	36
Cigarettes:		
1–15	18	60
16–25	135	33
26 and over	149	51

SOURCE: Rosenman, R. H. (115).

Lane, et al. (96) found significant relationships of smoking intensity and duration with personality factors—impulsiveness, emotional instability and belligerence scales.

Thomas (142) after reviewing various studies of psychological variables related to coronary heart disease, concludes that smoking may have different effects on different personality types and at different anxiety levels.

Multiple Risk Factors

The acceptance of a multiple factor causation hypothesis for coronary heart disease emphasizes the need for more sophisticated statistical analyses of appropriate data. Our understanding of the relative importance of various risk factors from the limited number of such special analyses has not been altered significantly from that obtained by more conventional statistical analyses (38).

Clarification of the apparent independence of several of the major risk factors has resulted.

Truett, et al. (145) emphasize that the major risk factors are noted to have a different order of importance by age and sex. Cigarette smoking is particularly important among younger males as noted in table 9.

(142) THOMAS, C. B. On cigarette smoking, coronary heart disease, and the genetic hypothesis. Johns Hopkins Medical Journal 122(2): 69–76, February 1968.

(38) EPSTEIN, F. H. Predicting coronary heart disease. Journal of the American Medical Association 201(11): 795–849, September 11, 1967.

(145) TRUETT, J., CORNFIELD, J., KANNEL, W. A multivariate analysis of the risk of coronary heart disease in Framingham. Journal of Chronic Diseases 20: 511–524, 1967.

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Review of Psychological and Personality Variables. The sentence describing the (143) Thomas article does not do justice to her excellent discussion. The article is reproduced in its entirety because it discusses another way of interpreting association between cigarette smoking and coronary heart disease.

ON CIGARETTE SMOKING, CORONARY HEART DISEASE, AND THE GENETIC HYPOTHESIS[1]

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What is the basis for the association between cigarette smoking and coronary heart disease? Although coronary disease is the most frequent cause of death in the United States today, and the majority of men smoke cigarettes, the answer to this question is still obscure. In 1956, Doll and Hill reported a significant statistical relationship between cigarette smoking and death from coronary disease which has been confirmed by other prospective studies (1–8). The difference between smokers and nonsmokers in respect to coronary disease mortality is relatively small, however, compared to the ten- to twentyfold differences often noted in respect to deaths from lung cancer in the prospective studies reviewed by the Advisory Committee to the Surgeon General of the Public Health Service (9, page 161, Table 5). In contrast, the median mortality ratio for coronary disease was 1.7 (range 1.5 to 2.0) for seven prospective studies of smokers and nonsmokers (9, page 323).

Many people have concluded that a causal relationship between cigarette smoking and coronary disease has, therefore, been established, but some have pointed out that such an association could be equally well explained on the grounds that 1) smokers are constitutionally different from nonsmokers, so that smoking cigarettes gives them more of a physiological or psychological boost and 2) cigarette smokers are more often the precoronary type of individual than nonsmokers. There have been scattered pieces of evidence that this may, indeed, be the case (10–16). At the time of the Surgeon General's report, these were sufficient to warrant the statement that "male cigarette smokers have a higher death rate from coronary artery disease than non-smoking males, but it is not clear that the association has causal significance." (9, page 327).

In examining the evidence that the statistical association between cigarette smoking and coronary heart disease may not be a simple cause-and-effect relationship, two facets of the genetic hypothesis,

1) that cigarette smokers are constitutionally different from nonsmokers, and
2) that individuals with a high risk of developing coronary heart disease are constitutionally different from those with a low risk,

can profitably be considered together. Although the implications are basically genetic, the term "constitutional" is used here rather than "genetic" because most measurements of adult men, whether physical or psychological, represent the phenotype, or manifest characteristics of the individual resulting from the interaction of his genotype, or genetic make-up, and the environment. The degree to which the environment interacts with the genetic component varies greatly according to the trait under consideration and the particular external circumstances. Certain traits, such as the blood groups, are not known to be modifiable by natural means. Others, such as stature, are modified only under

[1] This work was supported by Research Grant HE-01891, National Institutes of Health.

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such adverse conditions as severe undernutrition, while the proportionate roles played by genetics and environment in such characteristics as body weight, arterial blood pressure, total serum cholesterol level and personality structure are still being vigorously debated (17–29). While the genetic hypothesis does not necessarily contradict the various environmental hypotheses, it does limit them and diminish their importance by asserting that not all individuals are equally susceptible to adverse environmental influences.

Reports of actual genetic studies in this area are limited in number. Differences have been found in the distributions of such genetic markers as the blood groups and the ability to taste phenylthiourea (P.T.C.) in populations of smokers and nonsmokers; these findings are in harmony with the genetic hypothesis (12, 15). Twin studies carried out abroad point in the same direction. Monozygotic twins showed a higher degree of concordance than dizygotic twins in regard to smoking habits (30). In monozygotic twins with discordant smoking habits, coronary disease was not more frequent among the smokers than among the nonsmokers (31, 32). The numbers involved in these comparisons were too small, however, for definitive statistical evaluation.

Somatic variables reported to show statistically significant smoker-nonsmoker differences range from a series of anthropometric measurements to resting heart rate and blood pressure (13, 14, 16). The mean differences in all of these comparisons have been small, however, and at times have varied in direction from study to study, as in the case of weight (14, 16). Moreover, the small circulatory differences observed could well be the *result* of the smoking habit rather than a true constitutional difference.

Perhaps the most thought-provoking smoker-nonsmoker differences lie in the psychological area. There is a considerable body of evidence to show that the personality of smokers differs from that of nonsmokers in important ways (33–38). In the words of Eysenck, 1) "smokers tend to be more emotional, more neurotic, more given to anxieties, more tense, more likely to suffer from the so-called psychosomatic symptoms" than nonsmokers, and 2) "smokers tend to be more extroverted, nonsmokers more introverted.—Extroverted people tend to be sociable, to like parties, to value good food, drink and the good things of life generally—to take risks more readily, to act without regard to consequences, and to find it difficult to stick to the same task day after day" (39). Schubert has emphasized the point that the smoker seeks physiological, social and psychological arousal (40). His findings among college students, based on the Minnesota Multiphasic Personality Inventory, revealed that, compared with nonsmokers, smokers more frequently describe themselves as 1) being bored and seeking thrills, 2) behaving in a socially unacceptable fashion, and 3) having masculine traits. Smokers also scored higher on an impulsivity scale.

Work from our own laboratory indicates that psychological smoker-nonsmoker differences are of considerable importance. As part of a long-term prospective study of the precursors of hypertension and coronary disease, discriminant function analysis was used to test the hypothesis that cigarette smokers are different from nonsmokers in a number of psychobiological ways (41). The overall differentiation between nonsmokers and two groups of cigarette smokers in a population of male medical students was found to be highly significant.

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Cigarette smokers had substantially greater *anxiety* scores[2] than nonsmokers; *heart rate* and *anxiety* showed the greatest discriminatory powers among the seven variables used. *Cholesterol* and *pulse pressure* contributed to the differentiation to a lesser degree, with *anger* close behind. These findings, taken with those of others cited above, suggest that outstanding characteristics differentiating cigarette smokers from nonsmokers reside in the realm of personality.

It was, therefore, intriguing to find that *anxiety* was the most important variable in a similar discriminatory analysis based on parental history of coronary heart disease (43). Virtually the same population and variables were used; in particular, the measure of *anxiety* employed in the two analyses was identical. Again, the overall differentiation was highly significant. On the average, the group with *fathers* affected by coronary heart disease reported a *higher* anxiety level than did the group with both parents unaffected, whereas the group whose *mothers* had coronary heart disease had *lower* anxiety scores than the group with two unaffected parents. *Depression* was significantly less evident in both positive-parent groups. Although they aided in the discrimination, *anger, diastolic pressure, height* and *cholesterol level* made much smaller contributions.

From these two discriminatory analyses, several striking points emerge:

1. the same psychological characteristic, *anxiety,* was an important single variable in differentiating cigarette smokers from nonsmokers and in distinguishing subjects with a positive parental history of coronary disease from subjects without such a history,
2. the two criterion groups of smokers, which were selected on a quantitative basis in respect to number of cigarettes smoked a day, did *not* have significantly different characteristics from each other, and
3. the two groups with a positive parental history of coronary disease fell on opposite sides of the negative parental coronary disease group in respect to their mean anxiety scores.

Since a rather simply-derived anxiety scale proved to be a highly significant variable in both the smoker-nonsmoker differentiation and the discrimination between groups with and without parental coronary disease, the interesting possibility is raised that the link between cigarette smoking and coronary heart disease has to do with *anxiety* under stress. Does other research about the coronary personality tend to support this hypothesis?

More than twenty years ago, Dunbar described the personality profile of patients with coronary occlusion as one of compulsive striving, with an urge to get to the top through hard work, self-discipline and mastery of others (44). Her sub-

[2] Anxiety scores were based on the answers given by 1085 medical students to a questionnaire specially devised for the Study of the Precursors of Hypertension and Coronary Disease (41, 42). The questionnaire consists of a list of 25 habits of nervous tension (HNT); the subject was asked to check all the reactions or types of behavior characteristic of him when under stress. Patterns of response to stress were determined by means of a phi correlation matrix; scales were derived from the HNT items showing the highest degrees of association with each other. The reactions comprising the anxiety scale consist of *anxious feelings, general tension, difficulty sleeping, loss of appetite, tremulousness* and *urge to confide*, all of which showed significant positive correlations, and *urge to eat*, which was negatively correlated (41, p. 180). The anxiety scale scores, therefore, ranged from +6 to −1.

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jects were hospitalized patients under the age of 55. She came to her conclusions through psychiatric interviews supplemented by the Rorschach Test.

Since that time, there has been little agreement in regard to a psychodynamic personality pattern associated with coronary disease (15). There are some indications, however, that there may be *two* major coronary personality patterns which are diametrically opposed to each other. Bahnson and Wardwell, using home interviews plus self-administered check lists, studied 32 white men aged 35–64, who had survived their first attacks of myocardial infarction, and compared them with a control group (16). They found some differences between the coronary patients and the control group in respect to their feelings and attitudes toward their parents. The coronary group, however, resolved itself into two discrete subgroups which were almost the opposite of each other: the self-oriented, regressive type corresponding to the mother-oriented coronary patient ($N = 19$) and the socio-centric and controlled type corresponding to the father-oriented patient ($N = 13$).

The mother-oriented group showed the following characteristics:

1. they identified with their mothers in terms of her personal manners and intimate behavior identification
2. they were among the younger coronary patients
3. they were passive, stating that they frequently day-dreamed or "sat and did nothing", often lacking interest in and commitment to work
4. they showed dependency by tending to turn to others for help when in trouble
5. they were not compulsive and showed little concern over "face"
6. they had strong succorant needs
7. they had low ego strength and self-acceptance
8. they were unstable in that they often felt mixed-up, tense and worried
9. they showed a trend toward anxiety and depression
10. they frequently made use of regressive defenses
11. they showed insufficient control of aggression.

The father-oriented patients, on the other hand, showed the following characteristics:

1. they identified with their fathers through somatic and social image identification
2. they were among the older coronary patients
3. they were active and self-reliant
4. they showed strong compensatory socio-centric needs for achievement
5. they had considerable self-control and ego strength, with high self-acceptance and self-esteem
6. they clung to social norms
7. they had concern over "face"
8. they resorted frequently to the use of compulsive and repressive defenses in order to perform as solid citizens in spite of an unsatisfactory underlying self-image
9. their social commitment represented a flight from themselves.

Both the mother-oriented and the father-oriented coronary patients were considered by the authors to have failed in establishing their own identities in a satisfactory manner.

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In 1964, Ostfeld and his co-workers reported a four-year follow-up of a prospective epidemiological study of coronary heart disease in which the Minnesota Multiphasic Personality Inventory and the 16 Personality Factor Questionnaire were used to obtain measures of personality in men 40–55 years of age at the start (47). They found personality differences between the 48 men who, since being registered in the study, had developed symptoms of angina pectoris and the 37 men who had had myocardial infarctions. (They did not give the mean ages of their groups). On the average, the 1771 men who had remained free of clinical coronary disease showed personality profiles which lay *between* the angina pectoris group and the myocardial infarction group. Their findings indicated that the men in the angina group complained significantly more about somatic symptoms of all sorts and worried significantly more about the state of their health, even in the absence of objective findings, than the men in the infarct group. The angina group also reported greater lability in cardiovascular functioning and greater emotional lability and suggestibility. When the non-coronary group was compared with the total coronary group, no significant differences were found in their MMPI scores, but the 16 PF indicated that the coronary group were more independent in their social relationships, more suspicious of the motives of other people, and had greater feelings of inner tension.

A prospective study of coronary heart disease was initiated in 1960 by the Western Collaborative Group (8). Friedman and Rosenman, the leaders, had previously described an oral psychological questionnaire by which the specific behavior pattern of a subject could be classified as Type A or Type B. They considered that Type A was the coronary behavior pattern. It is characterized by excessive drive, aggressiveness, ambition, competitiveness and a sense of time urgency. They described Type B, on the other hand, as the relative absence of these characteristics. Answers to this questionnaire were part of the comprehensive data collected at intake on over 3,000 subjects. After two years, 54 of 1,584 Type A men and 16 of 1,593 Type B men had developed coronary heart disease, more than a threefold difference. After four and a half years, there is still a predominance of the Type A behavior pattern among the subjects who developed coronary disease, but the difference is less striking (48). It should be noted that a substantial number of Type B men *did* develop coronary disease; again the evidence suggests that at least two precoronary personality types are involved.

That there are at least two major types of coronary disease has been suggested by clinical studies, also. In two groups of men dying from coronary heart disease, for example, those diagnosed as having coronary disease at their last periodic health examination were compared with those whose heart disease was undetected at that time (49). The latter group was younger, and contained nearly twice as many heavy cigarette smokers and nearly twice as many men with hypercholesteremia as did the group with diagnosed heart disease. The facts that 1) both hypercholesteremia and heavy cigarette smoking have been more closely associated with death from coronary disease at younger than at older ages (cf. Table 20, p. 1105, ref. 6, 8, 49); 2) the anxiety-linked "coronary personality" was more often found in younger coronary patients by Bahnson and Wardwell, and 3) the preponderance of new coronary events in Type A subjects was greatest in

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Rosenman and Friedman's youngest age group, all tend to support Oliver's statement, "Indeed, there may be at least two major types of coronary disease—one associated with an active metabolic disorder and another associated with advancing age" (50).

Much remains to be done before the psychological factors underlying either the smoking habit or the coronary diathesis are fully understood, but it looks more and more as if the *kind of person* one is has to be taken into account. Whereas a decade ago, Hammond said, "there is as much reason to suppose that cigarette smoking causes nervous tension as to believe that nervous tension causes cigarette smoking," it now seems possible that both statements are true, but for different types of men, so that one uses smoking as an energizer, the other as a tranquillizer (51). Our own findings and those of others point to the existence of distinctive personality traits in cigarette smokers, on the one hand, and in precoronary individuals and coronary patients on the other. Inasmuch as a specific pattern of *anxiety* under stress was significantly related both to cigarette smoking and to parental coronary disease, *anxiety* appears to be one kind of common denominator (41, 43). In three studies, anxiety has been described as characterizing one of *two* groups of coronary patients or precoronary individuals—the *mother-oriented group* of Bahnson and Wardwell (46), the *angina group* of Ostfeld et al (47) and the *Type A behavior* pattern of Friedman and Rosenman (8). The familial occurrence of coronary heart disease has been documented, and points toward the involvement of genetic factors (52, 53). It seems likely that smoking habit patterns, too, are, to some extent, expressions of inborn differences. Intensive investigation of the sources and kinds of anxiety, and how destructive forms of anxiety can be identified and relieved may be the next important step in the prevention of coronary heart disease.

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Genetic and Constitutional Studies

Baer (*5*) found that heavy smokers among college males were taller than light smokers and nonsmokers. Lane, et al. (*96*) also found significant associations between body size measurements, including ponderal index (though not with height or weight individually), and amount of smoking in the study of over 675 aviators.

TABLE 9.—*Linear discriminant function coefficients (in standard units) for various risk factors in coronary heart disease, by sex and age: 12 Year Framingham Study*

Risk factors	Men				Women		
	Combined ages	30-37 years	38-47 years	48-62 years	Combined ages	30-47 years	48-62 years
Age	0.5031	0.2394	0.3331	0.2170	0.6239	0.7323	0.2600
Cholesterol	0.4444	0.9613	0.3207	0.3790	0.2941	0.7322	0.1207
Systolic blood pressure	0.3334	0.3127	0.1609	0.3509	0.5356	0.1917	0.4776
Relative weight	0.1890	0.1911	0.3619	0.1886	0.0975	0.0751	0.1481
Hemoglobin	−0.1049	0.0313	−0.0134	−0.2206	0.0392	−0.0301	0.0734
Cigarettes smoked	0.4192	0.6423	0.2681	0.3004	0.0625	−0.0731	0.1262
ECG abnormality	0.2626	0.2653	0.2556	0.2197	0.2015	0.2231	0.2526

SOURCE: Truett, J. (*15*)

Cederlof (*18*) has emphasized the value of studies of twins for investigating aspects of coronary heart disease and presents certain suggested modifications in methodology. The 1967 Report (*116*) discussed the studies by Cederlof on Swedish twin pairs (*19, 20*). His data on American twin pairs was recently presented and showed results similar to those of the Swedish twins (*18*).

The problems with interpretation of these studies are several. The small numbers of cases and the combining of data for both sexes in various subcategories make rates and ratios subject to significant chance variations. In addition, use of a questionnaire for angina, with only modest levels of reliability and validity requires a larger study population before definitive conclusions can be made. The lack of information on the distribution of risk factors other than smoking in subsamples of discordant twin pairs and the total group of twin pairs makes the comparison of ratios for prevalence of symptoms difficult to evaluate. The inclusion in the "smoking" group of those who had stopped smoking up to 3 years previous to the study, would also tend to diminish the differences between smokers and nonsmokers. Definitions of discordant smoking habits must conform to those differences identified as significant in the large-scale population studies.

The fact that discordance for smoking does occur among monozygotic twins certainly indicates that the smoking habit cannot be determined by genetic factors alone. Twin studies with further sophistication of design, larger number of cases, better definitions of disease, and more significant identification of discordant exposures have the potential of contributing substantially to our understanding of the interactive factors in coronary heart disease.

In an article reviewing some of the epidemiological evidence in the 3½ years subsequent to the 1964 report, Seltzer (*129*) concluded that there was no substantial evidence to indicate a further association of cigarette smoking with coronary heart disease beyond that stated in the 1964 report.

Seltzer alluded to what he called "inconsistencies" in the recent literature relating to duration, amount, age, inhalation and mode of tobacco smoking with coronary heart disease.

The addition of many more person years of experience, from the new and continuing studies, provides data since the 1964 Report that can be analyzed age-specifically. When this is done most of these "inconsistencies" disappear.

Seltzer's conclusion is contrary to that of most epidemiologists who are familiar with the current research. Furthermore, he has not considered the important relevance of the experimental, pathological, and clinical data that have been reported since 1964 concerning cigarette smoking and cardiovascular diseases.

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Seltzer's criticisms. The questions raised by (129) Seltzer have not been adequately answered by the 1968 document. The article is reproduced in its complete form.

An Evaluation of the Effect of Smoking on Coronary Heart Disease

I. Epidemiological Evidence

Carl C. Seltzer, PhD

In January 1964, the Surgeon General's Advisory Committee on Smoking and Health[1] in considering the available information on smoking and coronary heart disease (CHD) (International Statistical Classification [ISC] 420) reported that "male cigarette smokers have a higher death rate from coronary artery disease than nonsmoking males, but it is not clear that the association has casual significance."

Three points should be noted. First, the committee left no doubt that there was a consistent statistically significant association among cigarette smokers of increased mortality and morbidity from CHD in men, particularly during middle life. Seven large completed or current prospective studies of smoking and death rate gave a CHD median mortality ratio (current cigarette smokers to nonsmokers) of 1.7, with no significant excess deaths among cigar and pipe smokers. Second, the committee recognized that certain factors other than smoking were known or thought to predispose to the condition or to be also associated with an increased incidence. Included among these were age, sex, morphological constitution, heredity, occupations involving responsibility and stress, low levels of physical activity, diets high in saturated fats, high blood pressure, high serum cholesterol levels, and excessive obesity. Third, the point was made that if it could be shown that cigarette smokers and nonsmokers had significant constitutional differences apart from any differences that might be caused by smoking itself, then the possibility would exist that some predisposition of smokers to the disease might also be of constitutional origin and not caused by smoking. After reviewing some of this evidence, the committee concluded, "In spite of some bits of suggestive evidence the existence of basic constitutional differences between smokers and nonsmokers is not presently established."

The Surgeon General, Luther Terry, MD, on Jan 29, 1964, speaking of CHD stated, ". . . the committee was unable to reach a firm conclusion as to the role smoking plays in causing or precipitating a death from this disease. We need to find out for sure whether smoking is a factor in this disease or whether it should be exonerated . . . we have no real clues as to what it is in tobacco that influences coronary artery disease, if indeed it does."[1]

Since publication of the Surgeon General's Report on Smoking and Health in early 1964, there have appeared many statements with regard to the

See also pages 139 and 201.

relationship of cigarette smoking and CHD which go far beyond the limited conclusions of the Surgeon General's Advisory Committee and the then Surgeon General. Some of these statements come from US Public Health officials, from responsible persons in medicine and science, and from numerous medical societies throughout the country, as well as many other sources. For example, in 1965 it was stated, "Ultimate elimination of cigarette smoking . . . would mean the saving of some 250,000 Americans from premature deaths caused by or associated with cigarette smoking . . . half of these premature deaths associated with cigarette smoking are due to cardiovascular diseases, particularly

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coronary artery disease. . . ."[4][5][6] In 1965, it was affirmed that ". . . the association [American Heart Association] believes that there is a total of approximately 250,000 excess premature deaths associated with cigarette smoking each year in the United States, and that of those, about 125,000 are associated with cardiovascular disease, principally coronary heart disease. . . . We have excellent evidence that heavy cigarette smoking, a pack or more a day, particularly accelerates atherosclerosis, and accentuates its effects, makes it worse. This accounts for the increased premature deaths that are associated with cigarette smoking so far as coronary artery disease is concerned."[7][8][9][10] In 1966 it was said, "In view of the mountain of evidence now available this is no longer a 'controversial' matter. The massive evidence indicating that cigarette smoking is a major coronary risk factor in middle-aged Americans and British men have been reviewed in many places . . ."[11] Again in 1966, it was declared ". . . unforgiveable for us to write off the 48 million adults in the United States who are now cigarette smokers. After all, these are the people in whom the extra hundreds of thousands of premature deaths will be occurring each year for the next 20 or 30 years; these are the people who suffer from . . . the 300,000 extra coronaries . . ."[12]

From the statements, ". . . it is not clear that the association has causal significance" and ". . . the committee was unable to reach a firm conclusion as to the role smoking plays in causing or precipitating death from this disease . . ." of the Surgeon General and his Advisory Committee on Smoking and Health in January 1964, we have since been presented with "131,000 excess deaths," "125,000 excess premature deaths," "300,000 extra coronaries" each year that are "caused by" or "associated with cigarette smoking."

Attention should be focused on the phrases "caused by" and "associated with cigarette smoking." These phrases clearly imply that the consequences of smoking cigarettes is a variable amount of excess premature CHD deaths. But no such implication can be drawn from the conclusion of the Surgeon General's committee of 1964. The latter reported a higher death rate from CHD *among male cigarette smokers* than among nonsmokers. If one were to transcribe this statement in terms of "excess deaths," then it could be stated that there was an excess of CHD deaths *among cigarette smokers* than among nonsmokers. To shift from excess deaths *among* cigarette smokers to excess deaths *associated with cigarette smoking* is to attribute *causality* to cigarette smoking, an attribution which the advisory committee was unable to reach.

We have no reason for assuming that what we are dealing with here is a matter of semantics. Rather, the more likely event is that these statements causally linking mortality from CHD among cigarette smokers must represent conclusions reached by some from new evidence available since the issuance of the advisory committee report in 1964. It becomes important, then, to inquire into the nature of this new evidence. At the same time, it is necessary to inquire into the availability of additional new evidence bearing upon the question of genetic and constitutional factors between smokers and nonsmokers, particularly insofar as they are related to the etiology of coronary heart disease.

Some readers may object to the use of the phrase "caused by," since the words "cause and effect" are extremely difficult to define clearly. In using these words, we are following the practice of the Surgeon General's 1964 report, which attempted to explain (pp 20-21) the meaning which that committee attached to the term causality. In stating "cigarette smoking is causally related to lung cancer in men," the Surgeon General's committee implied that cigarette smoking increases the probability that lung cancer will develop in a man. With regard to cardiovascular disease, the committee stated, "it is not clear that the association has causal significance," implying that the evidence available to them was insufficient to judge whether cigarette smoking is an effective agent in increasing the probability of death from cardiovascular disease or not.

Purpose of the Report

The purpose of this report, then, is to review the more important publications dealing with smoking and CHD which have appeared subsequent to the Surgeon General's Report on Smoking and Health in 1964, to answer the following question:

What is the nature of the additional evidence on smoking and CHD which has resulted in the magnification and extension of the claims of the effects of cigarette smoking on mortality and morbidity from CHD?

This particular communication (part 1) will consider the epidemiological evidence only and is limited to data on men. Subsequent reports covering experimental and clinical data, and constitutional and genetic evidence are planned.

This analysis of the epidemiological evidence was submitted for publication almost simultaneously with the appearance of *The Health Consequences of Smoking*, a Public Health Service review published in late 1967.[13] Accordingly, this is an independent analysis and does not contain references to or comparisons with the 1967 report.

The Material

In the 3½ years since publication of the Surgeon General's report of 1964, a certain amount of epidemiological research has been completed or continued in this country or abroad. For the purpose of this report, consideration has been given to the more pertinent studies as follows: Doll and Hill study of British doctors,[14] the combined Albany and Framingham study,[15] Dorn's US veterans study,[16] Hammond's prospective study,[17] the Canadian veterans study,[18] the Evans County, Georgia study,[19] the Tecumseh, Michigan prospective

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study,[14] Reid and co-workers' migrant study,[15] the health insurance plan (HIP) studies,[16,17] and the national health survey.[7]

These investigations are not always comparable, since their study designs lead to incidence rates of disease manifestations in some and to prevalence rates of disease or illness disability in others. Incidence rates of mortality or morbidity derived from longitudinal prospective or retrospective studies may be quite a different matter than prevalence rates of disease, illness, or disability derived from cross-sectional studies of whatever nature. These distinctions are important and must be kept in mind in assessing the respective findings in these studies, especially in connection with mortality ratios computed from different base lines. The first four studies listed above are prospective studies of mortality or morbidity with attendant death rates or incidence rates of disease manifestations in large populations, and hence have certain elements of comparability. On the other hand, for example, the national health survey is a prevalence study and does not identify the rate at which various types of morbidity develop in differential groups in the population but simply reports the recent existence of illness or disability, or both. As such, its findings under certain conditions may be spurious and at best are supportive in nature when they identify relationships previously established in incidence studies.

(It is to be noted, however, that "surprisingly good agreement" between prevalence and incidence results was found by the Framingham heart study with respect to relative risks for CHD.)[18]

While all of these investigations deserve detailed individual analyses of their findings, the limitations of space do not permit such elaboration. Many important discrepancies or inconsistencies (as well as consistencies) in various aspects of these studies are overlooked when the results of the studies are characterized solely by their main conclusions. A topical analysis of important aspects of the studies affords a productive approach to an understanding of the relative consistency of the results of the investigations.

Epidemiological Data Published Since Surgeon General's Report of 1964

The more important new evidence relative to mortality and morbidity from CHD is summarized according to the following subject categories: (1) overall mortality and morbidity in smokers and nonsmokers, (2) morbidity from angina pectoris, (3) mode of tobacco smoking, (4) age of smokers, (5) amount of cigarette smoking, (6) duration of cigarette smoking, (7) inhalation, and (8) disease rates in ex-smokers in relation to the duration of the cessation of smoking.

Overall Mortality and Morbidity in Smokers and Nonsmokers.—The Surgeon General's 1964 report concluded that male cigarette smokers have a higher death rate from CHD than men who did not smoke. All the new evidence gives the same results, a *confirmation* of the earlier findings. This is not surprising, since the conclusions of the 1964 report were based on "seven large completed or current prospective smoking and death rate studies." Additional new prospective studies or the extension of observations on previously reported current studies on the same or similar populations would not be expected to give different results. Similarly, all the new evidence on morbidity, with the exception of the Tecumseh study of Epstein et al,[19] confirms the existence of higher CHD prevalence rates among smokers than among nonsmokers. It is not clear why the Tecumseh study CHD prevalence rates are higher in nonsmokers than in smokers at every age level up to 70 years.

The new evidence does not change the basic nature of the association of higher CHD death rates in cigarette smokers. It simply confirms the previous evidence. The new data, either through longer observation periods of follow-up of ongoing studies or through additional studies of large populations, in the main merely serve to provide an opportunity for a more precise look at various interrelationships. Furthermore, there has been no change in the intensity of the association, such as would be suggested if the new data showed consistently higher average CHD death rates for smokers compared to nonsmokers than did the older data. But this has not been the case. The Surgeon General's 1964 report indicated a median mortality ratio of 1.7 among persons currently smoking cigarettes. It is seldom noted, however, that the Doll and Hill study of British doctors' (one of the key mortality studies) showed a 33% greater mortality rate for cigarette smokers from "CHD without hypertension" than nonsmokers, a figure far below that of most other prospective studies. But in the main, the average value of the mortality ratio in the new studies is approximately that found in the older evidence.

Angina Pectoris.—The Surgeon General's 1964 report makes brief mention of the fact that "angina pectoris . . . is less closely associated with cigarette smoking than is myocardial infarction." Available new mortality data support the conclusion that cigarette smokers have higher death rates associated with myocardial infarction than nonsmokers. But the new data appear to be ambivalent with respect to angina pectoris.

The combined Albany and Framingham study[20] clearly shows no significant increase in incidence of angina among cigarette smokers compared with nonsmokers. It was even found that the morbidity ratio (Framingham series) for those who smoked 20 or more cigarettes per day (78) was below that of the non-cigarette smokers (86). The conclusion arrived at was that "The risk of angina pectoris as the sole or initial manifestation of CHD appears to be unrelated to the tobacco habit." On the other hand, both the HIP[17] and Reid and co-workers' migrant[15] studies gave opposite results. The HIP

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study (based on incidence) reported a statistically significant association between cigarette smoking and angina pectoris among men. The authors of this study, however, caution that, "variations in methodology and diagnostic criteria may explain this departure from other studies' observation of no difference in risk for angina among cigarette smokers and nonsmokers." The migrant study, based on prevalence of angina-like symptoms, is in agreement with the results of the HIP study. It is quite probable that Epstein et al's Tecumseh study[13] also provides evidence of an absence of association between smoking and angina pectoris, since their data showed a slightly lower prevalence of CHD (angina pectoris or electrocardiographic signs of myocardial disease) in smokers.

It should be pointed out, in further reference to angina pectoris, that Cederlof et al,[14] in a study of morbidity among monozygotic twins from Sweden, found a similar frequency of angina pectoris among smokers and nonsmokers, a finding in general agreement with the data of the combined Albany and Framingham study.

Uncomplicated angina pectoris comprises about 20% of all manifestations of CHD in men; elimination of such cases would mean elimination of a significant segment of CHD cases from consideration of being related to the tobacco habit.

Mode of Tobacco Smoking.—The Surgeon General's 1964 report pointed out that ". . . the association of coronary disease with the use of tobacco in other forms [apart from cigarettes] has not been striking." All the new evidence with regard to pipe and cigar smokers showed little or no increase in their death rates from CHD over that of nonsmokers. In the case of the Doll and Hill study of British doctors,[8] pipe or cigar smokers gave a lower death rate than the group of nonsmokers. In the Dorn study of US veterans,[11] the mortality ratios of persons who smoked cigars or a pipe were virtually the same as that of nonsmokers. The Hammond study of American men[15] showed pipe smokers on the whole had lower CHD death rates than nonsmokers, while the cigar smokers tended to have slightly higher rates than the nonsmokers.

Overall, it may be said that the new evidence appears to establish a lack of association of excess deaths due to coronary heart disease among pipe or cigar smokers, a less qualified finding than given in the 1964 report. CHD disability, on the other hand, may show slightly higher frequency in pipe or cigar smokers than nonsmokers.

The fact that there appears to be no evidence for excess CHD death risk among pipe or cigar smokers is a matter of considerable importance. This result from epidemiological surveys is a disquieting finding to those engaged in the study of the effects of tobacco smoking on health. For the most part, the problem has been simply ignored, perhaps in the hope that somehow or other it would just disappear by itself. But the discordance of an excess mortality due to CHD in cigarette smokers but not in cigar or pipe smokers cannot be summarily swept under the rug.

Nicotine in the tobacco smoke is regarded by many as the agent responsible for the effects on coronary heart disease. However, this discordance in disease effects is inexplicable in terms of amount of nicotine and other constituents of tobacco smoke. The 1964 report stated, "Calculations indicate that the nicotine absorbed (40 to 60 mg) from six cigars equals that from 30 cigarettes inhaled." The Doll and Hill study of British doctors showed no significant differences among cigarette smokers between the CHD death rates of inhalers and noninhalers.[8] We know very little about the possible mechanisms which might explain why cigarette smokers have greater CHD death rates than nonsmokers while pipe and cigar smokers do not.

At the present stage of our knowledge, this anomaly is inexplicable. It is clearly a subject for further research. For now, we can only conclude that this discrepancy between the mortality rates of cigarette smokers vs those of cigar or pipe smokers is difficult to reconcile with the concept that tobacco smoking is causally related to excess deaths due to CHD.

Age of Smokers.—Virtually all the new studies confirm the finding of the 1964 report that death rates from coronary heart disease are relatively higher in male cigarette smokers compared to nonsmokers in middle age than in old age. In general, cigarette smokers more than 65 years of age have lower CHD mortality ratios and disabilities than those less than 65 years of age. This may, in part, reflect a selective survival effect in smokers and/or a diminishing risk for CHD among cigarette smokers relative to other influencing factors with advancing age.

It is possible that the relatively greater CHD mortality ratio among younger smokers is more a function of the differential age changes in CHD death rates of nonsmokers than of smokers. The point can be illustrated by comparing the CHD death rates according to age of smokers and nonsmokers with those of the general US population. In the US population in 1964, the death rate due to CHD of men ages 55 to 64 was 2.6 times greater than that of men ages 45 to 54, 2.2 times greater in ages 65 to 74 than in ages 55 to 64, and 1.9 times greater in ages 75 to 84 than in ages 65 to 74.[11] In comparison, Dorn's data[11] on veterans currently smoking cigarettes showed CHD death rate for men ages 55 to 64 to be 2.5 times greater than that of men ages 45 to 54, 1.9 times greater for ages 65 to 74 than ages 55 to 64, and 1.6 times greater in ages 75 to 84 than in ages 65 to 74. Further, in nonsmokers ("never smoked or occasionally only") from Dorn's study of veterans, CHD death rate for ages 55 to 64 was 10.0 times greater than that of ages 45 to 54, 2.0 times greater in ages 65 to 74 than in ages 55 to 64, and 2.2 times greater in ages 75 to 84 than in ages 65 to 74.

From these data, it would appear that the successive decade age increases in CHD death rates of

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the smokers parallel those of the US general population much more closely than do rates of the nonsmokers, with the nonsmokers particularly diverging from the general population in a far greater increase in CHD death rate from ages 45 to 54 to ages 55 to 64. Furthermore, in Dorn's study of veterans, the death rates for smokers are somewhat lower than those of the general public, and the death rates of persons who do not smoke are still lower. While it is difficult to make direct comparisons of death rates from one population to another, is it possible that the nonsmokers represent a very special and markedly singular group in the population, more so than the smokers?

Amount of Cigarette Smoking.—The Surgeon General's 1964 report states, ". . . the ratio of smokers' coronary death rates to those of nonsmokers increases progressively with the daily cigarette consumption." This increase in CHD death rates with increased amount of smoking was found in a number of studies.

However, an examination of the new data since the 1964 report reveals a very complex and hardly consistent picture. To begin with, a consistent positive gradient of CHD mortality with amount of cigarettes smoked is found only in the Dorn study,[11] Reid and co-workers' migrant study[14] (in British and Norwegian born but not in native born US men), and in white men of high social class in the Evans County, Georgia study.[15] "There is certainly no clear gradient [of CHD mortality] with number of cigarettes smoked" is the report by Doll and Hill in their survey of British doctors (a rising gradient is apparent in younger but not in older men), and no clear gradient is found in the Canadian veterans study,[13] and in the Negro and white men of low social class of the Evans County, Georgia study.[15]

Significantly, the majority of the new studies show inversions or inconsistencies in the gradient of mortality or morbidity with average number of cigarettes smoked daily. While it is true that in virtually all these instances, those who smoked the most cigarettes give consistently higher CHD and myocardial infarction rates than those who smoked the least, the consistency of the gradient is broken down as between the groups which smoked the least and the intermediate groups, with the intermediate rates the same or lower than the rates of the groups which smoked the least. Inversions between the groups which smoked the least (usually less than a pack a day) and the intermediate groups (at least one pack but less than two packs daily) are to be found in the combined Albany and Framingham study,[17] the Hammond study,[12] Reid and co-workers' migrant study (native born subjects),[14] the HIP investigation,[18] and the national health survey.[19]

Accordingly, it cannot be said that the new data confirm the results of the 1964 report with respect to a consistent rising gradient of CHD mortality with increased amounts of cigarettes smoked. On the contrary, the new data, with its many inconsistencies and inversions in the "rising gradient," indicate that this whole subject is not as clear cut as it appeared at first blush.

Parenthetically, it is to be noted that almost identical inversions in body build measurements according to amount of cigarettes smoked have been described by Seltzer in his study of morphological constitution and smoking habits of Harvard college graduates.[20]

Duration of Cigarette Smoking.—The 1964 report made no comment with regard to duration of smoking and CHD rates. Since the 1964 report, there have been three important studies which have dealt with this subject. The combined Albany and Framingham study[17] found an absence of association between duration of heavy cigarette smoking and risk of myocardial infarction. In Dorn's US veterans study there was also no significant relationship between duration of cigarette smoking and risk of death from CHD; Kahn summarized this by stating that there was ". . . an almost perfect fit of the data with a hypothesis of no relationship to duration."[11] And in the Canadian veterans survey there was no clear gradient of increasing CHD mortality with increasing years of smoking experience.[13] In fact, in this material, the mortality ratios for heart and circulatory diseases for those who had smoked cigarettes for 30 to 39 years (1.5) were lower than those of individuals who had smoked for a period of only 5 to 9 or 10 to 14 years (1.7 and 1.8, respectively).

It is notable that while duration of cigarette smoking is considered an important factor in connection with lung cancer mortality, the new evidence since the 1964 report points to an exoneration of this important element with respect to CHD. The evidence would appear to be consistent with the conclusion of the authors of the combined Albany and Framingham study that it is ". . . not any cumulative effect of inhaling cigarette smoke which precipitates myocardial infarction and death from CHD. . . ."[16]

This has led to the suggestion by the Framingham heart study that coronary heart disease is only *acutely* connected with cigarette smoking not *chronically* connected, acting by the "triggering of a lethal arrhythmia or thrombosis in subjects predisposed by an already compromised coronary circulation."[17] If this is indeed true, then the effect of smoking (by their suggestion) would be limited solely to those persons with "already compromised circulations." Does this signify that cigarette smoking is without deleterious effect on those with a normal, healthy coronary apparatus?

Inhalation.—The Surgeon General's 1964 report states, ". . . at each level of consumption the ratio (mortality ratio) increases with amount of inhalation reported by the smokers."

On this subject the new data give conflicting results. In the Doll and Hill study of British doctors,[13] the authors stated, "Only small and statis-

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tically insignificant differences were observed in coronary disease without hypertension (3% excess in inhalers). . . ." Furthermore, the death rate for noninhalers (5.09) was substantially higher than that for nonsmokers (3.29). We should not lose sight of this latter point. If more extended observations of British doctors beyond the present ten years' observations tend to confirm this finding, this would make it appear that something else apart from the inhalation of cigarette smoke is responsible for the higher death rate from CHD of smokers over nonsmokers. In this regard, other known risk factors and constitutional differences between smokers and nonsmokers would have to be given more serious consideration in the totality of the problem than has been accorded them up to now.

Hammond's prospective study,[13] on the other hand, exhibited a tendency for CHD death rates to increase with degree of inhalation. The data might have been more illuminating, however, if the noninhalers had not been lumped together with those who inhaled slightly. Again we find that Hammond's subjects who did not inhale or inhaled slightly had much higher death rates than the nonsmokers.

Ex-Smokers.—The 1964 report points out that, "men who stop smoking have a lower death rate from coronary disease than those who continue," and cites the six-year experience of the combined Albany and Framingham study[7] and Hammond and Horn's[11] 44 months follow-up of more than 187,000 American men.

The studies since have added considerably more material, but the nature of the results can hardly be said to clarify the subject. Thus, while Doll and Hill's study of British doctors,[8] Dorn's study of US veterans,[10] the Hammond study of American men,[12] and the study of Canadian veterans[11] give lower CHD rates for ex-smokers than of those currently smoking cigarettes, higher CHD rates are found among ex-smokers than among those currently smoking cigarettes and nonsmokers in the Tecumseh, Michigan study,[17] Reid and co-workers' study of migrants,[16] and the national health survey.[18] The combined Albany and Framingham study[19] shows former cigarette smokers with a lower CHD death risk than nonsmokers, and about the same level of CHD risk for fatal and nonfatal myocardial infarction as between former cigarette smokers and nonsmokers. The authors state, "The risk of CHD or death for ex-cigarette smokers in these two populations (Albany and Framingham) was nearly equal to the risk for those who never smoked . . ."

The mortality ratios of ex-cigarette smokers found in Dorn's data recede to an intermediate position between the corresponding figures for current smokers and nonsmokers, and that former cigar and pipe smokers have higher mortality ratios than those who continue smoking (as Dorn had reported earlier)." Dorn had suggested that many smokers may have stopped smoking because of ill health, but did not understand why this should be true for cigar and pipe smokers but not for cigarette smokers. For this reason, Kahn excluded from his calculations those individuals who had stopped smoking because of doctors' orders, but the effect persisted among cigar and pipe smokers just the same. Kahn does not find "obvious" why this effect persists. Some complications were also apparent in the Hammond study.[12] Ex-cigarette smokers who quit recently (less than one year ago for those who formerly smoked 1 to 19 cigarettes a day and less than five years ago for those persons who smoked 20 or more cigarettes a day) had CHD death rates as high as or higher than persons currently smoking cigarettes. This seemingly anomalous finding was further investigated in another study by Hammond and Garfinkel[14] in which ill health was suggested as a complicating factor in stopping smoking or reducing cigarette consumption. They reported that the bias introduced by the influence of ill health on smoking habits "makes it difficult to evaluate the degree of benefit derived from giving up smoking, and even more difficult to determine whether giving up the habit results in a reduction of death rates soon after."

Further conflicting results are to be found with respect to the first years after smoking is stopped and the long-term cessation of smoking. A sharp fall in CHD mortality is seen in the Doll and Hill study[8] in the first five years after the subjects stopped smoking (followed by a rise in the next period), but only moderate declines are to be found in the early years following discontinuance of smoking in Dorn's US veterans[10] and Hammond's American men.[12] The CHD rates of ex-smokers, after the longest period of cessation of cigarette smoking, fall to a level *below* that of persons currently smoking cigarettes but still *higher* than nonsmokers in the Doll and Hill,[8] Dorn,[10] and Canadian veterans studies,[11] and in the Hammond survey of the category of persons who smoked 20 or more cigarettes a day.[12] In the Hammond study, the CHD death rate dropped to the level of nonsmokers for the persons who smoked 1 to 19 cigarettes a day.

The extreme difficulties, in these kinds of studies, of clearly unraveling the effect of discontinuance of cigarette smoking on CHD rates is recognized by Doll and Hill,[8] Kahn,[13] Hammond and Garfinkel,[14] Epstein et al,[15] Reid et al,[16] K[illegible][17] and others. Doll and Hill, who gave much attention to this subject, pointed out, for example, that much of the fall of mortality with discontinuance of smoking ". . . may be an artifact, due merely to the selective failure of doctors to give up smoking when they are already ill."[8] Epstein et al, in explanation of their higher CHD rates of ex-smokers relative to both current smokers and nonsmokers, have said that their finding ". . . is to be expected, since persons with disease are more likely to discontinue the habit."[15] They all make the point that

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the bias introduced by ill health on smoking habits "dirties up" the data of ex-smokers and makes it therefore difficult to establish clear-cut trends and effects.

Summary

With this presentation of the additional information since the Surgeon General's 1964 report on the subject of smoking and coronary heart disease (considering the epidemiological studies only), we are now able to assess the nature of the evidence which has led to the extension and magnification of the claims of the effect cigarette smoking has on mortality and disability from CHD made by numerous people.

The conclusion of the Surgeon General's 1964 Report that male cigarette smokers have a higher death rate from CHD than men who do not smoke has been confirmed in the new studies published since the report was issued. This conclusion must be accepted as an established observation. But the question still remains as to the interpretation to be given to this statistical observation. The most such an epidemiological observation " . . . can do is to demonstrate the existence of a relationship between cigarette smoking and various health characteristics; it cannot establish any existing relationship as a causal one,"[5] and ". . . inferences on causality cannot depend on the demonstration of association alone."[6] The first phase of the epidemiological approach to a disease problem is the determination of the statistical association; the second phase is the derivation of biological inferences from the pattern of statistical association."

What inferences, then, may be drawn from the additional epidemiological evidence which has appeared since the 1964 report? And particularly, since the 1964 report concluded ". . . but it is not clear that the association has causal significance," what new inferences may be drawn with respect to causality?

Our survey of the new epidemiological evidence has indicated that, for all practical purposes, pipe or cigar smoking is not associated with excess deaths and disabilities due to coronary heart disease (CHD), leaving cigarette smoking as the focus of necessary attention. The weight of evidence, at the moment, is that angina pectoris as the sole or initial manifestation of CHD is probably unrelated to cigarette smoking. There are still some lingering questions with regard to the prevalence data in this regard, but conclusions drawn from prevalence data are generally considered less reliable than incidence rates. This would leave myocardial infarction (and sudden deaths) as the principal conditions statistically associated with cigarette smokers. In this connection, Doll and Hill have pointed out that a relationship with smoking is characteristic of only a little more than one-half the total number of deaths attributed to coronary thrombosis.[7] This erosion of postulated CHD smoking risks is further enhanced by the Framingham heart study which suggested that the effects of smoking is limited to those persons with "already compromised circulations."

With respect to amount of cigarette smoking, the new data do not confirm the finding of the Surgeon General's report of a consistent rising gradient of CHD mortality with increased amounts of cigarettes smoked, but on the contrary give a complex and hardly consistent picture showing a profusion of inconsistencies and inversions. The new data have in effect raised serious questions as to the validity of the 1964 report on this point. Duration of cigarette smoking has been found to be unassociated with excess CHD mortality in cigarette smokers in the new data, and conflicting results are obtained with regard to the effect of inhalation. Finally, the new data dealing with the effect of discontinuance of cigarette smoking (a subject considered of such great significance in lung cancer mortality) frequently give contradictory and inconsistent findings, and pose a virtually insoluble problem as to valid interpretations and conclusions that may be drawn from such data in the present study designs. The bias introduced by the influence of ill health on smoking habits makes it extremely difficult to determine whether giving up the habit actually results in a reduction of death rates soon after. Accordingly, in some respects the epidemiological evidence is less clear now than at the time of the 1964 report.

It is, therefore, difficult to see from the new epidemiological data how valid causal inferences can be drawn that *cigarette smoking* is linked to excess CHD deaths or that the excess CHD deaths are "*caused by*" cigarette smoking. We do not know whether or not there is a causal connection between cigarette smoking and increased deaths from coronary heart disease.

The present state of our knowledge still suggests (as the Surgeon General's Advisory Committee's Report on Smoking and Health stated in 1964) that "male cigarette smokers have a higher death rate from coronary artery disease than nonsmoking males, but it is not clear that the association has causal significance."

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Epidemiological Studies

The results of epidemiological studies on the relationship of smoking to serum lipid levels have not been consistent. Several studies reported no significant difference in serum cholesterol (*56, 30, 61, 150*) and triglyceride levels (*30, 61*) between smokers and nonsmokers. In their study of twins, Blomstrand, et al. (*11*) state that prolonged smoking had an insignificant effect on all serum lipid levels in their monozygotic twins and only elevated phospholipids in their dizygotic group. However, they quote a personal communication from Carlson, et al. who found elevated trigyceride levels in smokers in a prospective study of 6,000 persons.

In a very comprehensive study of 637 former naval aviation cadets over a period of 23 years, Harlan, et al. (*56*) investigated the relationship of various constitutional and environmental factors to serum lipid and lipoprotein levels. They found that serum Sf 0–12 (beta) lipoproteins and cholesterol levels were related to cigarette smoking and that the duration of smoking also had a significant correlation. The authors felt that the relationship of smoking to these lipids was presumably direct, because cigarette smoking did not correlate with other factors related to lipids.

Experimental Studies—Animal

Studies in dogs of the immediate effects of tobacco smoke inhalation and nicotine administration showed an increase in serum triglycerides but not cholesterol, in addition to a rise in free fatty acids (*76*). There were no differences in cigarette, cigar or pipe smoke effects when the depth of inhalation was kept constant. Chronic administration of nicotine in dogs resulted in a 50 percent rise in serum cholesterol levels but did not affect triglycerides (*82*). Kershbaum, et al. (*83*) have also shown that pronethalol (a beta-receptor blocker) inhibits the serum-free fatty acid and triglyceride rise induced by nicotine in dogs.

In studies of the lipid and atherogenic effects of chronic nicotine administration in cholesterol-fed rabbits, one report found no effect in serum lipid levels but a significantly higher incidence of aortic fibrosis (*51*). Other investigators found that nicotine increased the amount of cholesterol in the blood and the intensity of lesions in the aorta (*23*). In cholesterol-fed rabbits administered vitamin D, Hass, et al. (*59*) found that nicotine induced severe calcific athero-arteriosclerosis and occlusive thromboarteritis, especially conspicuous in cardiac, smooth and skeletal muscle.

Astrup (*2*) has shown that in rabbits on a high cholesterol diet, chronic carbon monoxide exposure had a marked atherogenic effect.

Gudbjarnason (*52*) has shown that chronic nicotine administration in dogs leads to a diminution in the rate of cholesterol turnover.

Studies in Humans

It has previously been reported (*73*) that cigarette smoking mobilizes free fatty acids, resulting in increased plasma concentrations. It was also found that this effect of smoking was the result of increased sympathetic and adrenal activity initiated by the absorbed nicotine (*84*), the latter having no direct lipolytic action in adipose tissue (*35*). This response to smoking has now been confirmed by other investigators (*11, 30, 110*).

Studies in man, on the immediate effect of cigarette smoking, have shown no effect on serum concentrations of lipoproteins and lipoprotein lipids (cholesterol, phospholipids, triglycerides) (*73, 92, 116*). In a recent study, however, an increase in serum beta-lipoproteins was observed 10 minutes after smoking (*72*).

In a study of the comparative effects of cigarette, cigar and pipe smoking on free fatty acid mobilization and catecholamine excretion, cigarette smoking was found to have a much greater effect (*81*). Less nicotine absorption in cigar and pipe smoking, due to the absence of inhaling, was considered to be the explanation for the milder biochemical effects with these two forms of smoking (*80*). Kershbaum, et al. also compared the effects of various types of cigarettes on these parameters (*79*). They found no difference in free fatty acid and catecholamine response or nicotine absorption with several brands of filter and non-filter cigarettes. Cigarettes containing shredded lettuce leaf had no effect.

In other lipid studies it was observed that smoking might increase the tendency of human blood serum to crystallize cholesterol (*87*).

Kershbaum has also shown that cigarette smoking increases the blood steroid levels in humans (*86*).

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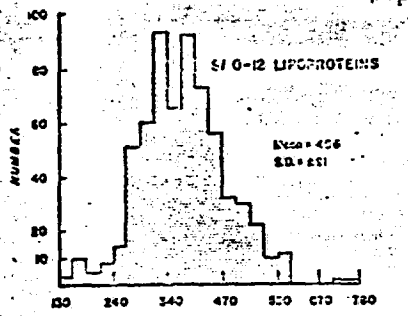
Epidemiological Studies Relating to Serum Lipids. Like other types of studies in this page, the epidemiological studies comparing nonsmokers and smokers indicate conflicting results. The negative studies are not discussed. The Results of (150) Van Buchem et al. are reproduced below.

The positive results of (56) Harlan et al. are described in the document. The differences in population and nature of diet may account for conflicting results. Note that Harlan et al. also identified skin folds, uric acid and weight gain to correlate with lipoprotein fraction.



Variable	Cumulative Multiple r
SMOKING - AMOUNT	0.144
SKINFOLDS - CHEST	.188
URIC ACID	.221
WEIGHT GAIN 24 - 45 yr. (-)	.241
Resting glucose	.252
Family history - father	.265
Mesomorphy	.267
Family history - mother	.274
PBI (-)	.278

FIGURE 1. Frequency distribution of values for Sf 0-12 (beta) lipoproteins and factors correlated with levels of these lipoproteins. Factors having correlations significant at 5% level or greater are spelled out in capital letters. Skinfolds are a measurement of subcutaneous adipose tissue at the site noted. PBI = protein-bound iodine. See text for description of analytical methods.

The Sf 0-12 lipoproteins (beta-lipoprotein), which are composed predominantly of cholesterol (51%) and phospholipid (25%) but little triglyceride (6%), are related to cigarette smoking, skinfold thickness of the chest, uric acid, and have a negative relation up to weight gained from age 21 to age 45. Although the number of cigarettes smoked was selected by this analysis, the duration of cigarette smoking also had a significant correlation, these variables being highly interrelated. Similarly, skinfold thickness of the chest and back are closely related, and selection of the chest measurement excluded that of the back. However, skinfold thickness in other areas was not related to these lipoproteins. The minor contribution of protein-bound iodine (PBI) to the multiple correlation is of interest because of the close relationship between pathological

TABLE XIV. Serum-cholesterol level in smokers and non-smokers

	Serum cholesterol (mg %)		
	0—209	210—249	>250
Non-smokers	32	44	41
Light smokers	18	14	10
Moderate smokers	70	76	60
Heavy cigarette smokers	96	123	127
Heavy cigar smokers	23	24	29
Heavy smokers	6	12	11
Heavy pipe smokers	11	20	11
Unknown	1	1	
Total	257	314	289

Several times the nature of the diet of all men was examined with different methods. No correlation was found between the nutrition and the serum cholesterol level. The diet of the men before they suffered from atherosclerotic complications was not different from the diet of the whole group. No correlation was found between smoking or non-smoking, and the degree of smoking, and the serum cholesterol content.

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The 1967 Report reviewed the effects of smoking on *in vitro* thrombus formation, varying platelet characteristics and other serum factors associated with blood coagulation. It is not in the scope of this report to go into a detailed analysis of blood coagulation and/or thrombosis. However, the role of smoking and blood lipids on thrombogenesis will be briefly discussed, as they relate to thrombosis and cardiovascular disease.

Catecholamines

The role of catecholamines (especially epinephrine) in thrombogenesis must be stressed (*111*). The nicotine-induced catecholamine release, which plays a major role in cardiovascular dynamics might also be the mediating factor in the relation between cigarette smoking and thrombosis. Ardlie (*1*) has shown that catecholamines enhance ATP or ADP induced platelet aggregation. ADP and noradrenaline in low concentration (up to 0.05 μg./ml.) were found to increase platelet mobility (*55*). The reverse was true in higher concentration. Rowsell (*123*) has shown increases in both thrombus formation in an extracorporeal system and clotting time in silicon-coated tubes with moderate doses of epinephrine. Large doses gave values closer to the control state. Besterman (*8*) has shown a diurnal variation in "platelet" stickiness which might be associated with diurnal variations in catecholamine release. Glynn (*48*) found no difference in platelet aggregation between smokers and nonsmokers.

Shimamoto (*133*) proposes that epinephrine has a primary effect on the arterial wall causing the release of a thromboplastin-like substance which then leads to increased platelet aggregation. An autopsy study in humans by Auerbach (*3*) showed increased fibrous thickening in the walls of arterioles and small arteries of 5 organs, in smokers as compared to nonsmokers. This effect might be secondary to platelet changes which then caused damage to the arterial wall. As discussed earlier in the study by Hass (*59*), in which rabbits on a high cholesterol and vitamin D diet were given nicotine, at the site of the occurrence of thrombus there was usually an inflammation of the arterial wall.

(*111*) MURPHY, E. A., MUSTARD, J. F. Smoking and thrombosis. In: Wynder, E. L. Hoffmann, D., editors. Toward a Less Harmful Cigarette. Bethesda, U.S. Public Health Service. National Cancer Institute Monograph 28, June 1968. (In press)

(*1*) ARDLIE, N. G., GLEW, G., SCHWARTZ, C. J. Influence of catecholamines on nucleotide-induced platelet aggregation. Nature (London) 212 (5060): 415–417, October 22, 1966.

(*55*) HAMPTON, J. R., MITCHELL, J. R. A. Effect of aggregating agents on the electrophoretic mobility of human platelets. British Medical Journal 1: 1074–1077, 1966.

(*123*) ROWSELL, H. C., HEGARTY, B., DOWNIE, H. G., MUSTARD, J. F., MURPHY, E. A. Adrenaline and experimental thrombosis. British Journal of Haematology 12(1): 66–73, 1966.

(*8*) BESTERMAN, E., MYAT, G., TRAVADI, V. Diurnal variations of platelet stickiness compared with effects produced by adrenaline. British Medical Journal 1: 597–600, March 11, 1967.

(*48*) GLYNN, M. F., MUSTARD, J. F., BUCHANAN, M. R., MURPHY, E. A. Cigarette smoking and platelet aggregation. Canadian Medical Association Journal 95: 549–553, September 10, 1966.

(*133*) SHIMAMOTO, T., ISHIOKA, T., Release of a thromboplastic substance from arterial walls by epinephrine. Circulation Research 12(2): 138–144, February 1963.

(*3*) AUERBACH, O., HAMMOND, E. C., GARFINKEL, L. Thickening of walls of arterioles and small arteries in relation to age and smoking habits. New England Journal of Medicine 278(18): 980–984, May 2, 1968.

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Blood Lipids

Conner, et al. (*26*) and Warner, et al. (*152*) have described various experiments in dogs and rabbits, in which infusion of long-chain saturated free fatty acids caused extensive thrombosis and death. *In vitro* coagulation and platelet aggregation were also increased. Long-chain unsaturated free fatty acids, however, did not have these effects although microscopic platelet aggregation was observed (*66*). *In vitro* studies have shown that linoleic and linolenic acids might have a protective effect against platelet aggregation induced by long-chain saturated fatty acids (*73, 101*).

The rise in plasma-free fatty acids which follows cigarette smoking was associated with increased platelet adhesiveness (*110*). The long-chain fatty acid-induced platelet aggregation was suggested to be due to ADP release from platelets (*58*). Harrison (*57*) suggests that *in vitro* platelet adhesiveness tests are influenced by ADP release from damaged red cells and that the platelet change might really be a reflection of red cell abnormalities.

Bray (*14*) found that coronary heart disease patients have an exaggerated platelet adhesiveness in response to ADP or ATP.

Several studies have shown disturbances in lipid and carbohydrate metabolism in coronary heart disease patients (*24, 55, 136*).

Kurien (*95*) postulates that the increases in free fatty acid levels immediately after either an acute myocardial infarction or cerebrovascular accident result from tissue anoxia with a secondary catecholamine release, which then leads to the increases in free fatty acids. Malhrotra (*103*) studied two population groups in India. There was no difference in the cholesterol, trigiyceride, and free or esterified fatty acid levels between the two groups. However, the incidence of coronary heart disease was much higher in the population whose diet and fat absorption predispose to an abundance of long-chain fatty acids.

A majority of coronary heart disease patients have an abnormal glucose tolerance test. In most of these patients there is a greater decrease in free fatty acids in response to glucose and a slower return to normal values (*24, 136*).

Soloff and Schwartz (*136*) have determined two subgroups of these patients: one "A", in which the free fatty acid response to glucose resembled a normal curve except for an exaggerated rise after 5 hours; another "B", in which the free fatty acid response to glucose resembled that of diabetics, there being a slower decrease and a subnormal return of free fatty acid levels after 5 hours. The significant effect, however, is that type "B" patients had a relative hyporesponse of stearic acid (long-chain saturated) decline with a relatively decreased rise in linoleic acid (long-chain unsaturated) after 5 hours.

These findings may be related to the effect of saturated and unsaturated fatty acids on blood coagulation and suggest further research to delineate the specific fatty acids elicited after smoking and in coronary heart disease patients.

Cardiovascular Response to Smoking and/or Nicotine

This section should be read in conjunction with the findings reviewed in the 1967 report.

Experimental Studies

Nadeau, et al. (*112*) cannulated the sinus node artery in anesthetized dogs and noted chronotropic changes in response to doses of nicotine ranging from 1.0 to 100 μg./ml. Intranodal atropine abolished bradycardia and intranodal propranolol or hexamethonium abolished tachycardia. Nicotine inhibited the effects of cervical vagus nerve stimulation without modifying the response to intranodally injected acetylcholine. Nicotine did not inhibit the effect of stellate ganglion stimulation. These results illustrate the varying effects of nicotine under experimental conditions on the complicated neural and humoral mechanisms affecting heart rate and rhythm.

(26) Connor, W. E., Hoak, J. C., Warner, E. D. Fatty acids and thrombus formation. In: Sasahara, A. A., editor. Pulmonary Embolic Disease. London, 1965. Pp. 50-58.

(152) Warner, E. D. Hoak, J. C., Connor, W. E. The role of fatty acids in platelet aggregation and thrombosis. In: Brinkhaus, K. M., editor. Platelets: Their Role in Hemostasis and Thrombosis. Chapter 21. Transactions of the Conference held under the auspices of the International Committee on Haemostasis and Thrombosis, Chapel Hill, North Carolina, December 1966. Pp. 249-259.

(66) Hoak, J. C., Warner, E. D., Connor, W. E. Platelets, fatty acids and thrombosis. Circulation Research 20(1): 11-17, January 1967.

(73) Ferr, J. W., Mac Aulay, L., Pirrie, R., Bronte-Stewart, B. Platelet-aggregation by phospholipids and free fatty acids. Lancet 1: 1289-1290, June, 10, 1965.

(101) Mahadevan, V., Sinon, H., Lundgren, W. O. Effects of saturated and unsaturated fatty acids on blood platelet aggregation *in vitro*. Proceedings of the Society for Experimental Biology and Medicine 121: 82-85, 1966.

(58) Haslam, R. J. Role of adenosine diphosphate in the aggregation of human blood-platelets by thrombin and by fatty acids. Nature (London) 202: 765, 1964.

(57) Harrison, M. J. G., Mitchell, J. R. A. The influence of red blood cells on platelet adhesiveness. Lancet 2: 1163-1164, November 26, 1966.

(14) Bray, C., McDonald, L. A new platelet defect in patients with ischaemic heart disease. British Heart Journal 28(3): 429, May 1966.

(24) Cohen, A. M., Sharaff, E. Carbohydrate metabolism in myocardial infarction. Behavior of blood glucose and free fatty acids after glucose loading. Diabetes 14(2): 84-93, February 1965.

(95) Kurien, V. A., Oliver, M. F. Serum-free-acids after acute myocardial infarction and cerebral vascular occlusion. Lancet 2: 122-127, July 16, 1966.

(136) Soloff, L. A., Schwartz, H. Relationship between glucose and fatty acid in myocardial infarction. Lancet 1: 449-452, February 26, 1966.

(103) Malhotra, S. L. Serum lipids, dietary factors and ischemic heart disease. American Journal of Clinical Nutrition 20: 463-474, May 1967.

(112) Nadeau, R. A., James, T. N. Effects of nicotine on heart rate studies by direct perfusion of sinus node. American Journal of Physiology 212(4): 811-816, April 1967.

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Blood Lipids and Platelet Aggregation. Most of the articles cited in this section do not relate to cigarette smoking or to nicotine. Out of the 17 articles, there is only one which describes the acute effects of smoking on blood lipids. There were 12 patients who took smoking tests and sham-smoking test. The document quotes only one part of the Conclusions. The other statements omitted relate to the "variable effect of smoking on platelet adhesiveness". It should also be noted that sham-smoking caused the same effects as smoking. The Discussion and Summary are as follows:

(170) Murchison and Fyfe 1966

Discussion

The significant rise in plasma-N.E.F.A. after smoking, with no significant alteration in cholesterol and triglyceride, confirms the findings of previous workers (Kershbaum et al. 1961). It is interesting that sham-smoking was followed by a similar rise in plasma-N.E.F.A. in 5 of the 12 tests. The fact that the rise followed a steady basal period suggests that the effect was due to sham smoking rather than repeated venepuncture, and might possibly be due to the embarrassment of puffing an unlit cigarette. The fact that sham smoking may produce physiological changes was recognised by Irving and Yamamoto (1963) in their investigation of the effects of cigarette smoking on cardiac output.

An increase in unsaturated fatty acids at the expense of saturated fatty acids has been found by other investigators when the total plasma N.E.F.A. is raised by stimuli other than smoking (Rothlin et al. 1962, Wood et al. 1965). It is somewhat surprising that the change after sham smoking was more striking than that after smoking, and that the change in pattern does not correlate well with the change in total plasma-N.E.F.A. level.

Some earlier workers reported that cigarette smoking elevated the blood-glucose (Lundberg and Thyselius-Lundberg 1931) but Rehder and Roth (1959) have suggested that the rise shown was due to stress rather than an effect of smoking. In our series the rise can be attributed to smoking per se.

The increased platelet count after smoking also seems to be a nicotine effect. This effect has previously been reported in an uncontrolled study by Grassi and Caltabiano (1956). The mechanism is obscure, but may be a result of adrenaline release (Vaughan-Jones et al. 1963).

Platelet adhesiveness is known to be increased after myocardial infarction (Macdonald and Edgill 1957) and in disseminated sclerosis (Caspary et al. 1965, Payling Wright et al. 1965) and, since fatty-acid abnormalities have also been demonstrated in these conditions (James et al. 1957, Thompson 1966), a relationship between platelet adhesiveness and serum-fatty-acids has been suggested. The proposal has been supported by the in-vitro work of Kerr et al. (1965), who showed that saturated fatty acids induced greater platelet aggregation than unsaturated fatty acids, some of which seemed to have an inhibitory effect. Our results show that when the blood-glucose remained constant there was a good correlation between the changes in platelet adhesiveness and the changes in N.E.F.A. When the blood-glucose also altered (in the smoking-test) the relationship between the changes in platelet adhesiveness and N.E.F.A. was less close. In this situation, the rise in blood-glucose seemed to have a suppressive effect on platelet adhesiveness, since there was a negative correlation between the changes in blood-glucose and platelet adhesiveness.

Bridges et al. (1965) showed that platelet adhesiveness increased after an oral glucose load, but he was unable to show a correlation between the rise in blood-glucose and the rise in platelet adhesiveness. This situation, however, is quite different to the present one in which endogenous glucose is being mobilised. Bridges et al. (1965) also showed that the addition of glucose in vitro resulted in an increase in platelet adhesiveness, but this is contrary to the work of Hellem (1960) who was unable to demonstrate any effect within the physiological range for glucose.

We have not confirmed the findings of Ashby et al. (1965) of a significant increase in platelet adhesiveness after smoking. Although 7 cases showed a considerable rise in platelet adhesiveness following smoking, in 5 others in whom there was a marked rise in glucose the platelet adhesiveness fell. This effect was more evident in 2 patients who felt nauseated at the end of the smoking-period and who showed the largest increase in blood-glucose in association with delay in N.E.F.A. rise. Since Ashby et. al (1965) only measured platelet adhesiveness it is not possible to explain the discrepancy between his results and ours. It may be, however, that in the non-fasting state the blood-glucose response to smoking is less striking. The somewhat surprising finding of a significant increase in platelet adhesiveness after sham smoking is clearly associated with the unopposed effect of the rise in N.E.F.A. on which we have already commented.

Summary

Platelet adhesiveness, blood-glucose and plasma-lipids were estimated in 12 patients before and after smoking and sham smoking. Cigarette smoking elevated plasma nonesterified-fatty-acid levels and resulted in an increase in the proportion of unsaturated fatty acids at the expense of the saturated fatty acids. Smoking was also followed by a significant rise in blood-glucose and a transient increase in the total platelet count. The variable effect of smoking on platelet adhesiveness seemed to be due to opposing actions of changes in nonesterified fatty acid and glucose levels. A rise in plasma nonesterified fatty acid was associated with increased platelet adhesiveness, whereas a rise in glucose inhibited platelet adhesiveness.

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Sleight (*135*) and Borgel, et al. (*7*) have demonstrated cardiovascular depressor reflexes in dogs elicited by nicotine stimulation of the surface of the left ventricle. Studies have been undertaken in dogs to determine the effect of beta-sympathetic receptor blockade by propranolol on the cardiac actions of nicotine. Westfall (*158*), Edmundowicz (*32*), Papacostas, et al. (*116*), Shanks (*131*) and Puri (*119*) have noted that propranolol can prevent the usual positive inotropic effects of nicotine or norepinephrine stimulation on the myocardium as well as the indirect beta dilator effects on peripheral vessels. This results proportionately in a greater increase in left ventricular afterload accompanied by a reciprocal decline of the velocity of myocardial fiber shortening (*129*). It was also noted that resulting unopposed alpha receptor activation by nicotine could lead to increased total peripheral resistance with impaired stroke volume and cardiac output. This is further evidence that catecholamines, the release of which is induced by smoking, intermediate the cardiovascular response to nicotine.

The effect of nicotine in single and repeated administrations was studied on the terminal vascular bed of the heart by Corsini, et al. (*27*). Results indicate that in dogs with intact coronary circulations, the single intravenous infusion of nicotine (150 ug./kg. body weight/minute) increased both the left ventricular capillary blood flow as well as the terminal vascular capacity; the chronic intramuscular administration (0.5 mg./kg. body weight given 3 times/day for 2 months), however, had no such effect. In contrast, in dogs with constriction of the coronary arteries, nicotine administration in either (single or repetitive doses) form resulted in a fall of capillary blood flow but an increase in the terminal vascular capacity. Capillary blood flow as measured in these studies represents a nutrient inflow to the myocardium. Nicotine administration resulted in an increase in both the velocity of myocardial shortening as well as the force of contraction, and these effects of nicotine are identical to those of norepinephrine. In addition, there was also an increase in the rate of left ventricular pressure rise (dp/dt) and a decline in left ventricular end-diastolic pressure (*121*).

Coleman, et al (*25*) studied isolated cat papillary muscles to determine the mechanism of the norepinephrine-induced stimulation of myocardial oxygen consumption. They found that norepinephrine does not increase the myocardial tissue oxygen demand unless contractility is increased, other factors being held constant. Norepinephrine is known to increase myocardial contractility.

Further studies (*49, 142*) on anesthetized open-chest dogs to determine the relative influences of changes in either the contractile state or in tension development on myocardial tissue oxygen consumption, indicate that both are significant factors. Basal oxygen requirements, activation energy, and the cost of contractile element shortening against a load appear to influence myocardial tissue oxygen consumption to a lesser degree.

Chidsey, et al. (*21, 22*) studied the relationship of norepinephrine to heart failure and the functional state of the human myocardium. They reemphasize the role of norepinephrine in altering myocardial fiber length and contractile status as demonstrated in human left ventricular papillary muscles removed from patients at the time of mitral valve replacement.

Ayres (*4*) has noted products of anaerobic cardiac metabolism in dogs made ischemic by exposure to carbon monoxide. These will be presented in a subsequent section of this chapter. Weissler, et al. (*156*), in experiments with isolated perfused rat hearts, have reported on the importance of glucose as a substrate for anaerobic metabolism of the heart subjected to anoxia for 30 minutes. When glucose was added to the anaerobic perfusate, the electrical and mechanical performance of the heart improved markedly, as did the recovery of the heart during the subsequent period of reoxygenation. Lactate production was fivefold greater in the glucose-supported anoxic heart than in the anoxic heart without glucose. In similar fashion, morphologic changes of the mitochondria and longitudinal tubules of the anoxic heart noted by electron microscopy, were averted by the inclusion of glucose in the perfusion fluid. This experiment suggests that glucose might help temporarily to prevent myocardial infarction, caused by relative myocardial anoxia, by providing a substrate for anaerobic cardiac metabolism.

(*135*) Sleight, P. A cardiovascular depressor reflex from the epicardium of the left ventricle in the dog. Journal of Physiology 173(3): 321-333, 1964.

(*7*) Borgel, D. H., Makin, G. S. Central and peripheral cardiovascular changes following chemical stimulation of the surface of the dog's heart. Cardiovascular Research 1(1): 58-70, 1967.

(*158*) Westfall, T. C., Cicolloni, P. B., Edmundowicz, A. C. Influence of propranolol on hemodynamic changes and plasma catecholamine levels following cigarette smoking and nicotine. Proceedings of the Society for Experimental Biology and Medicine 123: 174-179, 1966.

(*32*) Edmundowicz, A. C., Cicolloni, P. B., Perkins, K. E. Cardiovascular responses to cigarette smoke and nicotine in dogs following beta-adrenergic blockade with propranolol. (Abstract) Federation Proceedings 24: 713, March-April 1965.

(*116*) Papacostas, C. A., Reed, J. F. Influence of beta receptor blockade on certain cardiovascular actions of nicotine. Archives Internationales de Pharmacodynamie et de Therapie 164(1): 167-172, 1966.

(*131*) Shanks, R. G. The pharmacology of beta sympathetic blockade. American Journal of Cardiology 18(3): 338-346, September 1966.

(*119*) Puri, P. S., Alamy, D., Bing, R. J. Effect of nicotine on the contractility of the intact heart. Journal of Clinical Pharmacology, 1968. (In press)

(*27*) Corsini, G. C., Puri, P. S., Bing, R. J. Effect of nicotine on capillary flow and vascular bed of the heart in presence and absence of experimental coronary artery insufficiency. Federation Proceedings 27(2): 652, March-April 1968.

(*121*) Puri, P. S., Bing, R. J. Influence of cardiovascular drugs on the force-velocity relation of the intact heart. The Physiologist 10(3): 255, August 1967.

(*25*) Coleman, H. N., Sonnenblick, E. H., Braunwald, E. Mechanism of the norepinephrine-induced stimulation of myocardial oxygen consumption as studied in the isolated cat papillary muscle. Circulation (Supplement III) 36(4): 80, October 1967.

(*49*) Graham, T. P., Jr., Covell, J. W., Sonnenblick, E. H., Ross, J., Jr., Braunwald, E. Control of myocardial oxygen consumption: Relative influence of contractile state and tension development. Journal of Clinical Investigation 47: 375-385, 1968.

(*142*) Taylor, R. R., Cingolani, H. E., Graham, T. P., Clancy, R. L. Myocardial oxygen consumption: left ventricular fibre shortening and wall tension. Cardiovascular Research 1: 219-228, 1967.

(*21*) Chidsey, C. A., Braunwald, E., Morrow, A. G. Catecholamine excretion and cardiac stores of norepinephrine in congestive heart failure. American Journal of Medicine 39(3): 442-451, September 1965.

(*22*) Chidsey, C. A., Sonnenblick, E. H., Morrow, A. G., Braunwald, E. Norepinephrine stores and contractile force of papillary muscle from the failing human heart. Circulation 33(1): 43-51, January 1966.

(*4*) Ayres, S. M. Personal communication. March 1968.

(*156*) Weissler, A. M., Kecker, F. A., Baba, N., Scarpelli, D. G., Leighton, R. F., Gallishaw, J. K. Role of anaerobic metabolism in the preservation of functional capacity and structure of anoxic myocardium. Journal of Clinical Investigation 47: 403-416, 1968.

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Experimental Studies on the Heart. The lengthy discussion on cardiovascular response to smoking and nicotine which started in the preceding page and continued to the next page does not relate directly to the question of cigarette smoking. Most of the cited references are on catecholamines, carbon monoxide and hypoxia. There are only two references on cigarette smoke: (158) Westfall et al. and (32) Edmundowicz et al. relating to the release of catecholamines but the amount of cigarette smoke administered was excessive, since there was a significant rise in blood pressure (119 to 176) and slowing of the heart rate. There is no cited reference that catecholamines can be released by administration of ordinary amounts of cigarette smoke which does not influence blood pressure.

CARDIOVASCULAR RESPONSES TO CIGARETTE SMOKE AND NICOTINE IN DOGS FOLLOWING β-ADRENERGIC BLOCKADE WITH PROPRANOLOL (I.C.I. 45,520). A. C. Edmundowicz, P. A. Cipollone, and W. F. Penrod. West Virginia Univ. Sch. of Med., Morgantown, W. Va.

Eight anesthetized dogs were made to inhale smoke from cigarettes through a cuffed endotracheal tube; respirations were either spontaneous or controlled by a pump respirator. Smoking caused an increase in mean arterial pressure (A.P.) from 119 to 176 mm. Hg, a decrease of 41% in heart rate (H.R.), and increases of 72% in stroke volume (S.V.) and 34% in cardiac output (C.O.) (all mean values). Mean levels of epinephrine (E) and norepinephrine (N) in blood from the high inferior vena cava (I.V.C.) increased from <0.2 to 113 and from <0.2 to 23 γ/L respectively. Similar responses followed I.V. injections of nicotine. After β-adrenergic blockade with 0.2 mg./kg. propranolol I.V., smoking decreased H.R. by 22%, S.V. by 9%, and C.O. by 34%. Mean A.P. increased from 110 to 196 mm. Hg and several dogs developed transient left ventricular failure. Mean levels of E and N in the high I.V.C. increased from <0.2 to 145 and from <0.2 to 20 γ/L. Responses to nicotine following blockade were similar. Conclusion: β-adrenergic blockade by propranolol does not modify the release of catecholamines from the adrenal gland of dogs in response to smoking and nicotine; unmasking of α receptor activity causes severe hypertension and compromises left ventricular function. (Supported by USPHS Grant 07758-02).

The other experiments cited relate to nicotine. The significance of measurement of nutrient blood flow was not mentioned. Nicotine increases nutrient flow in a dog with coronary constriction indicating that there is adequate blood flow in the ischemic area following nicotine injection.

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The isolated perfused rat heart was also studied by Brachfeld, et al. (*12*) to determine the effects of nicotine on lysosomal, mitochondrial, and supernatant enzyme systems of the myocardium. They suggested that nicotine toxicity may be expressed in terms of damage to the lysosomal membrane and the cell wall. Shibata, et al. (*132*) studied the action of nicotine on the transmembrane potential and contractility of isolated rat atria. They suggest that while nicotine may influence membrane electrodynamics, there may also be a direct action on the contractile mechanism of the cardiac muscle cell by changing the duration of the action potential, which implies alterations in potassium fluxes.

Nicotine-induced changes, in dogs, in action potentials and conduction depression, with enhancement of Purkinje fibre "automaticity," may lead to the development of ventricular fibrillation (*50*). Post myocardial infarction dogs were much more sensitive to the administration of nicotine, as measured by electrocardiographic changes, than were normal dogs, especially in the acute stage of myocardial infarction (*6*). Webb, et al. (*154*) state that changes in fibrillation thresholds after cigarette smoking noted in dogs, by analogy, "may have relevance to the higher incidence of coronary deaths without increased incidence of angina in cigarette smokers."

Studies in Humans

The 1967 report noted that sudden death from previously undetected coronary heart disease appeared to occur frequently among cigarette smokers. Kuller (*94*) showed in a study of sudden death in Baltimore that arteriosclerotic heart disease was a major cause (61.4 percent) of death. No smoking histories were recorded. Luke, et al. (*99*) reviewed 275 consecutive autopsied cases of sudden unexpected death from natural causes, in individuals age 20 to 45 years, and noted that asymptomatic coronary artery disease comprised 25 percent of the causes of sudden death. Again, no smoking data were taken. Data pooled from 10 studies available to Burch, et al. (*17*), indicated that cardiovascular disease accounted for 51 percent of 8,151 adult sudden deaths.

Present clinical evidence indicates that ventricular asystole or fibrillation may be the mechanism of sudden cardiovascular death in most cases. It is known that hypoxia, hypercapnia, ischemia, electrolyte disturbances, and increased catecholamine activity all can predispose to ventricular fibrillation. From available physiological evidence noted elsewhere in this and the bronchopulmonary chapter, and also in the 1967 Report, it would appear that smoking can directly or indirectly contribute to the development of these predisposing conditions. It is well accepted clinically that ventricular, nodal, or atrial premature contractions can be increased or induced by cigarette smoking, as well as by other factors, and can be reduced by the cessation of cigarette smoking in both normal and ischemic hearts. These premature contractions are frequently precursors of their respective tachycardias. Also, a person with an acute or impending myocardial infarction subjected to the sympathoadrenal effect of smoking could more readily develop a fatal arrhythmia (*75*). The relationship of smoking to cardiac arrhythmias must be studied further to determine more exactly both the physiology and the mechanisms involved in sudden deaths from cardiovascular disease.

Kerrigan, et al. (*74*) studied cardiac output in both smokers and nonsmokers who had no evidence of coronary heart disease and found rises in cardiac output in response to exercise and to cigarette smoking separately and then in combination. They note that the total increase in cardiac output appears to be the sum of the exercise and the smoking effects. Smoking may create an additional myocardial tissue oxygen demand above and beyond the demand attributable to exercise.

Moses, et al. (*105*) reported that pretreatment of healthy normals with glucose blocks the increased cardiac output response to cigarette smoking by inhibiting the increases in stroke volume but not heart rate.

(*12*) Brachfeld, N., Kuehn, P., Kawade, M., Oran, E. Nicotine mediated release of myocardial cell and lysosomal enzymes. Annals of Internal Medicine 68(5): 1031, May 1967.

(*132*) Shibata, S., Hollander, P. H., Webb, J. L. Effect of nicotine on the transmembrane potential and contractility of isolated rat atria. Experientia 24(3): 236-237, 1968.

(*50*) Greenspan, K., Knoebel, S. B., Fisch, C. Effects of nicotine upon human and canine cardiac action potential and contractile state. (Abstract) The Project for Research on Tobacco and Health 1964-1968. American Medical Association Education and Research Foundation, June 1968. Pp. 24-25.

(*6*) Bellet, S., Kershbaum, A., Meade, R. H., Jr., Schwartz, L. The effect of tobacco smoke and nicotine on the normal heart and in the presence of myocardial damage produced by coronary ligation. American Journal of the Medical Sciences 201(1): 40-51, January 1941.

(*154*) Webb, W. R., Wall, S. D., Sproa, W. L. Cigarette smoke and fibrillation threshold in dogs. Clinical Research 16(1): 74, January 1968.

(*94*) Kuller, L., Lilienfeld, A. Epidemiological study of sudden and unexpected deaths due to arteriosclerotic heart disease. Circulation 34: 1056-1063, December 1966.

(*99*) Luke, J. L., Halpern, M. Sudden unexpected death from natural causes in young adults. A review of 275 consecutive autopsied cases. Archives of Pathology 85(1): 10-17, January 1968.

(*17*) Burch, G. E., DePasquale, N. P. Sudden, unexpected, natural death. American Journal of the Medical Sciences 249: 89-97, January 1965.

(*75*) Kershbaum, A. Personal communication. March 1968.

(*74*) Kerrigan, R., Jain, A. C., Doyle, J. T. The circulatory response to cigarette smoking at rest and after exercise. American Journal of the Medical Sciences 255: 113-119, February 1968.

(*105*) Moses, D. C., Powers, D., Soloff, L. A. Glucose blockade of the increase in stroke volume produced by smoking. Circulation 29(6): 830-834, June 1964.

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Sudden Deaths - The incorrect statement in the 1967 report on sudden death is discussed in page 360 (a). The additional references relating to sudden death have no smoking data but contain information of risk factors which contribute to sudden death. For instance (94) Kuller and Lilienfeld reported that approximately two-thirds of coronary deaths had a history of at least one of the following: diabetes, hypertension and cerebrovascular disease, and heart disease. The relevant table from the article is as follows:

Table 8

Distribution of Arteriosclerotic Heart Disease Deaths by Race, Sex, and Number and Percentage with a History of Heart Disease or Several Other Cardiovascular Diseases (CVD)

Race & sex	Category	Total deaths	History of heart disease		History of diabetes		History of hypertension		No history of at least one disease or CVD	
			No.	%	No.	%	No.	%	No.	%
WM	Sudden	392	209	53.3	46	11.7	93	23.7	126	32.1
	Not sudden	193	133	68.9	35	18.1	54	28.0	—	—
WF	Sudden	89	39	43.8	7	7.9	37	41.6	38	42.7
	Not sudden	76	49	64.5	29	38.2	47	61.8	—	—
NM	Sudden	114	64	56.1	16	14.0	29	25.4	37	32.5
	Not sudden	60	33	55.0	14	23.2	20	33.0	—	—
NF	Sudden	71	27	38.0	7	9.9	26	36.6	30	42.3
	Not sudden	52	34	65.4	17	32.7	15	28.8	—	—
Total	Sudden	666	339	50.9	76	11.4	185	27.8	231	34.7
	Not sudden	381*	249	65.3	95	24.9	136	35.7	—	—

*Excludes 51 not-sudden deaths when the patient had been admitted to the hospital with a noncardiovascular disease and subsequently had a new coronary event in the hospital.

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Frankl, et al. (42) noted that after 5 normal male chronic smokers were given propranolol, cigarette smoking caused a significant increase in systemic blood pressure and a significant decrease in cardiac output. Thus cigarette smoking after propranolol administration may be especially hazardous. Yamamoto noted similar results (160).

Sen Gupta, et al. (130) studied 11 ischemic cardiac patients and 14 healthy controls for abnormal ECG changes after smoking one cigarette and noted specific or nonspecific changes in almost all of the cardiac patients as compared to few changes in the healthy smokers and no abnormalities in the healthy nonsmokers. Pentecost, et al. (117) studied the acute effects of cigarette smoking in patients with angina or post-myocardial infarction as compared with normal controls. Normal men and those with angina in the absence of infarction behaved similarly with an increase in pulse rate, mean pressure, stroke volume, and cardiac output. The majority of the patients among the post-myocardial infarction group showed a marked fall in stroke volume and cardiac output while smoking. In another study (43) to evaluate the interrelationship of smoking and exercise effects on cardiac output, a fall in cardiac output that occurred in some post-infarction coronary patients as a result of smoking alone was noted. Also noted were decreases in cardiac output after smoking and exercising as compared to post-exercise cardiac output in the same patients before they smoked.

Starr (139) suggests that the ballistocardiographic (BCG) findings in cardiac disease and after cigarette smoking may provide valuable information about the rate of acceleration of myocardial contractile velocity that cannot be determined by studying cardiac output or stroke volume alone. A diseased heart has a slower accelerative rate of contraction. BCG abnormalities have frequently been related to cigarette smoking in subjects with or without heart disease, including angina pectoris. The BCG findings of Jackson, et al. (68) indicate that cigarette smoking itself may have acute and chronic harmful effects on myocardial function, since duration of smoking was also correlated with certain abnormalities.

Gazes, et al. (47), Braunwald, et al. (13), and Klensch, et al. (91) have found higher plasma norepinephrine levels in coronary patients at rest and after smoking as compared to normals. Kershbaum, et al. (77) have reported that the rise in free fatty acids after cigarette smoking is also greater in patients with coronary heart disease, probably due to an enhanced norepinephrine response.

Burch, et al. (16) also stress the importance of the action of norepinephrine on the venous vascular system. "Greater than 70% of the blood volume is contained within the systemic venous system and a 10% reduction in venous capacity would result in the sudden shifting of 350 ml. of blood (assuming a blood volume of 5 L.) centrally into the pulmonary veins and atria. In the presence of a diseased left ventricle, such a sudden increase in central blood volume may result in acute left ventricular failure" (17). (Additional cardiopulmonary considerations are noted in the bronchopulmonary disease chapter of this Report).

Human Myocardial Tissue Function in Relation to Anoxia and to Carbon Monoxide

Likoff, et al. (96) suggest that an oxygen-diffusion impairment or inappropriate oxygen utilization at the myocardial microcirculatory or cellular level could be responsible for the anginal symptoms and ECG signs of apparent myocardial ischemia in the presence of adequate arterial saturation and patent coronary arteries by coronary arteriography. Ayres (7) and Eliot (57) suggest that these mechanisms may be related to the carbon monoxide effect and abnormal hemoglobin function.

In addition to a review of the coronary circulation as related to myocardial ischemia and angina pectoris, Elliott, et al. (55) studied zonal myocardial ischemia (60) by ECG, coronary angiography and regional lactate metabolism in 50 patients with proven coronary heart disease. They found that the ECG findings could be normal even when severe coronary disease was present with myocardial production of lactate. The regional lactate pattern was very helpful in determining the location of myocardial ischemia and significant coronary artery lesions.

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Exercise and Smoking in Post-Infarction Patients. The statements relating to (43) Frank et al. are incorrect. A fall in output was noted in 2 patients (-2 and -18%) and a rise in 6. The authors state "Smoking failed to produce the striking increase in output seen in young, healthy, habitual smokers." Furthermore, exercise and smoking caused an increase in output less than that seen in pre-smoking state. The Results and Summary are as follows:

Table 1

Findings before Smoking

Patient	Age	SA	Rest CO	Rest CI	Rest SV	Rest HR	Exercise CO	Exercise CI	Exercise SV	Exercise HR
S.C.*	64	1.55	2.84	1.84	50	57	4.52	2.92	54	84
W.E.*	62	1.90	3.82	2.04	57	66	5.10	2.71	57	90
E.F.*	53	1.56	3.85	2.46	64	60	6.88	4.41	82	84
C.C.*	69	1.51	2.55	1.67	35	72	4.04	2.67	46	87
M.H.*	55	1.64	2.69	1.64	45	60	3.62	2.20	38	96
A.J.*	48	1.92	3.83	1.99	71	54	7.87	4.08	82	96
A.L.†	56	1.99	3.50	1.76	56	63	7.66	3.85	91	84
F.L.†	68	1.75	3.44	1.97	60	57	5.44	3.11	60	91

* Chronic smokers.

† Nonsmokers.

SA, surface area in M^2; CO, cardiac output in L./min.; CI, cardiac index in L./min./M^2; SV, stroke volume in ml.; HR, heart rate in beats/min.

Table 2

Findings after Smoking

Patient	Rest CO	Rest %Δ	Rest CI	Rest %Δ	Rest SV	Rest %Δ	Rest HR	Exercise CO	Exercise %Δ	Exercise CI	Exercise %Δ	Exercise SV	Exercise %Δ	Exercise HR
S.C.*	2.78	−2.1	1.79	−3.2	44	−12.0	63	3.93	−12.6	2.55	−12.6	42	−22.2	93
W.E.*	4.10	+7.3	2.20	+7.8	52	−8.8	78	5.90	+15.7	3.10	+14.4	58	+1.75	102
E.F.*	4.10	+6.5	2.63	+6.9	57	−10.9	72	5.52	−19.8	3.54	−19.0	68	−17.0	81
C.C.*	4.68	+45.5	3.10	+46.1	46	+23.9	102	4.45	+10.1	2.95	+10.5	48	+4.4	93
M.H.*	2.19	−18.5	1.33	−18.8	37	−17.7	60	—	—	—	—	—	—	—
A.J.*	4.44	+15.9	2.31	+16.0	55	−22.5	81	7.47	−5.1	3.89	−4.6	57	−34.1	132
A.L.†	4.03	+15.1	2.02	+14.9	58	+3.6	63	7.94	+3.6	3.99	+3.6	95	+4.4	84
F.L.†	3.96	+15.1	2.26	+14.7	55	−12.0	72	6.48	+19.1	3.70	+19.0	58	−3.3	111

*Chronic smokers.

†Nonsmokers.

CO, cardiac output in L./min.; CI, cardiac index in L./min./M^2; SV, stroke volume in ml.; HR, heart rate in beats/min.; %Δ, Per cent change from nonsmoking state.

Summary

Smoking by subjects with healed myocardial infarction, in contrast to its effects on the normal subject, fails to provoke an increase in cardiac output or in stroke volume. On the other hand, smoking does increase the heart rate in subjects with healed myocardial infarction. This dissociation between the effect on heart rate and on cardiac output and stroke volume, which was also noted in the healthy subject pretreated with glucose, indicates that increase in heart rate is mediated by different factors than those that increase stroke volume and cardiac output.

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In studies of coronary patients exposed to relatively low levels of carbon monoxide, Ayres (7) has reported that myocardial lactate and pyruvate extraction decreased or shifted to actual production, suggesting the presence of anaerobic metabolism. These data support his previous findings noted in the 1967 report that carboxyhemoglobin can interfere with oxygen delivery to the myocardium to the degree that relative myocardial anoxia can occur. The shift to anaerobic cardiac metabolism, which is relatively ineffective as a source of energy, indicates the presence of myocardial anoxia, and should be regarded as a warning sign. In these same experiments Ayres has noted that the myocardial oxygen extraction is decreased in response to carbon monoxide inhalation, and thus has further demonstrated the relationships of carbon monoxide with relative myocardial anoxia and anaerobic myocardial metabolism. The shift to the left of the hemoglobin-oxygen dissociation curve, describing the decreased ability of hemoglobin to release oxygen at the tissue level, is directly related to increased carboxyhemoglobin levels.

The animal experiments of Weissler (*159*), noted in the previous section, suggest that glucose might possibly help to temporarily prevent myocardial infarction from relative myocardial anoxia, by providing a substrate for anaerobic metabolism. Since myocardial ischemia may be caused not only by complete coronary arterial obstruction, but also by increased myocardial tissue oxygen demand above and beyond available oxygen supply, it would be important to know whether cigarette smokers have more products of anaerobic myocardial metabolism than do nonsmokers.

Eliot (33) has noted apparent hemoglobin abnormalities in patients with signs of myocardial ischemia or acute necrosis, and in smokers as compared to controls. However, he suggests that there are other hemoglobin abnormalities also present besides the well documented carboxyhemoglobin abnormalities associated with the carbon monoxide effect of cigarettes. Some reverted to normal hemoglobin status after stopping smoking.

Anomalous hemoglobin-oxygen dissociation was noted in "heavy" cigarette smokers (more than one pack per day) without known coronary heart disease. In experiments where the amount of cigarette smoking was controlled, there appeared to be a threshold effect: more than 12 cigarettes per day caused this anomalous dissociation to occur (53). Birnstingl (9) reports finding an increased hemoglobin affinity for oxygen in smokers, which does not appear to be explained solely by the increased carboxyhemoglobin levels in smokers.

Research to further study the interrelationships of carbon monoxide to the myoglobin of heart muscle should be performed because it is possible that carbon monoxide may replace oxymyoglobin with carboxymyoglobin and disturb the oxygen-dissociation phenomena of myoglobin (88, 126, 159). The limitations of blood supply and the high energy output of heart muscle as compared to skeletal muscle may make the myoglobin impairments by carbon monoxide of possible etiologic importance in cigarette smoking and heart disease.

Hydrogen cyanide appears to be rapidly converted to thiocyanates by the body, but the absorption by the lung of cyanide from cigarette smoke might possibly result in higher serum cyanide levels in the coronary arteries than in the systemic circulation. As noted in the 1964 Report, the cyanide ion is capable of stopping cellular respiration abruptly through inactivation of cytochrome oxidase. In sublethal exposures, the cyanide ion is gradually released from its combination with the ferric ion of cytochrome oxidase, converted to thiocyanate ion and excreted in the urine. Thiocyanate blood levels in smokers are three times higher than in nonsmokers and relative differences in urinary excretion are even more pronounced. Cytochrome oxidase is very important in cellular respiration of all body cells. In view of the extremely high myocardial cellular needs for aerobic metabolism, it is possible that the cyanide ion inactivation of cytochrome oxidase also can occur in myocardial cells and be of critical importance, especially in light of other risk factors such as impaired coronary blood flow, the carbon monoxide effect, and the known increases in myocardial tissue oxygen demand caused by the smoking/nicotine-induced catecholamine release. Further research is needed to determine whether or not cyanide ions in concentrations equivalent to those found in cigarette smokers, have a harmful effect on the myocardium, in terms of both acute and chronic exposures.

(33) Eliot, R. S., Mizukami, H. Oxygen affinity of hemoglobin in persons with acute myocardial infarction and in smokers. Circulation 34: 331–336, August 1966.

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Anomalous hemoglobin-oxygen dissociation. The 1968 document has misquoted (9) Birnstingl et al. The authors explain the increased hemoglobin affinity for oxygen in smokers as almost entirely due to carbon monoxide. Portions of the Discussion and Summary are as follows:

> **The Effect of Smoking.**—The increase in oxygen affinity found in smokers appeared mainly due to high concentrations of carbon monoxide in the blood of the smokers (Haldane-Smith effect). When the oxygen saturation values had been corrected for HbCO content, the mean oxygen affinity of the group of smokers was much reduced, but it remained significantly above that of the group of non-smokers. This small residual increase remains unexplained. It is unlikely to be due to methaemoglobin, as this was estimated in a few of the samples and the concentrations were found to be low (less than 2 per cent).

SUMMARY

A study has been made of the effects of age, smoking, and Buerger's disease on oxyhaemoglobin dissociation.

Healthy male subjects over 40 years of age have a blood oxygen affinity which is greater than that of a similar group under this age. This would result in a shift to the left of the oxyhaemoglobin dissociation curve.

Cigarette smokers also have an increased oxygen affinity, but this is almost entirely due to a raised carbon monoxide haemoglobin level.

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Glucose Metabolism and Possible Cardiovascular Effects

Epstein (*37*) has reviewed the relationships of hyperglycemia to coronary heart disease. Although he states that there appeared to be no relationship of cigarette smoking to the hyperglycemia that was associated with the prevalence of coronary heart disease in the Tecumseh population, Higgins (*63*) reports that the Tecumseh cigarette smokers, both male and female, had approximately a 10 mg. percent elevation in blood glucose as compared to nonsmokers, although the percentage elevations above the median levels were not statistically significant. Since Epstein (*37*) reported that cigarette smokers in the Tecumseh study population had a higher incidence of coronary heart disease, it would be interesting to see what the interrelationship of the incidence of coronary heart disease is to the cigarette smokers who have elevated blood glucose levels.

Cohen, et al. (*24*) have reported abnormal glucose tolerance in some postinfarction patients, suggesting the possibility that this group has difficulty utilizing glucose. It is known that smoking induces release of catecholamines which can create an increased demand for glucose by the body. Wahlberg (*152*) had noted that in patients with atherosclerotic disease but without clinical diabetes mellitus, the glucose tolerance was pathologic in 46 percent as compared with 10 percent of controls, and normal in 33 percent as compared with 71 percent controls. From this he infers that subclinical diabetes mellitus may predispose to vascular disease in the same way as clinical diabetes mellitus.

Kingsbury, et al. (*89*) studied a small group of male patients with peripheral arteriosclerotic disease to determine the serum glucose, nonesterified fatty acids, and immunoreactive insulin responses to subcutaneous adrenaline and to smoking. Under basal conditions, the fatty acid response was normal. While adrenaline consistently caused a rise in serum glucose, cigarette smoking either had no effect or lowered the fasting concentration. In 5 patients smoking caused an elevation in the immunoreactive insulin which could not be explained by blood sugar changes. The implication is that these patients were hypersecretors of insulin. Unfortunately, detailed smoking histories are not available for these individuals. Szanto (*141*), in a very small study of habitual smokers, noted a "hyperinsulinism" response during oral glucose tolerance testing after smoking two cigarettes. This response was markedly reduced when the test was repeated after a 14-day abstinence from smoking. The view that hyperinsulinemia is associated with atherogenesis has been suggested (*114, 118, 149, 157*) and discussed by Mahler (*102*). If smoking directly or indirectly causes a hyperinsulin response in some individuals, then this may possibly be one mechanism by which cigarette smoking may enhance atherogenesis.

Kershbaum, et al. (*86*) have noted higher plasma 11-hydroxy corticosteriod levels in smokers. Whether the "hyperinsulinism" reported to be present in smokers is related to increased adrenal corticosteriods remains to be determined. Hyperinsulinism could be a response to the frequent catecholamine-induced hyperglycemia caused by cigarette smoking in individuals without significant clinical or subclinical coronary heart disease; but conceivably the hyperinsulinism response might be more pathological in coronary patients. Also, the potassium and other ion changes caused by glucose shifts in response to shifts in insulin levels may predispose to cardiac arrhythmias and sudden death.

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Hyperinsulinism. This page devoted to glucose concludes with the thesis that hyperinsulinism is a link between smoking and atherosclerosis. All the references do not relate to smoking except (141) Szanto, who has published two letters in the British Medical Journal (16 April 1966 and 15 July 1967). The work cited in the second letter has not appeared in a regular article.

Smoking and Atherosclerosis

SIR,—In a previous letter on this subject (16 April 1966, p. 984) I suggested that smoking and dietary sugar affect the arteries in a similar way. Further work with the help of heavy-smoker volunteers indicates that the atherogenic effect of smoking might lie in its ability to induce hyperinsulinism. This conclusion is based on the following experiment.

Twelve male and seven female volunteers were chosen with the only criterion in their selection that they habitually smoked 20 cigarettes, or more, per day. Their ages ranged from 25 to 57 years. After explaining the purpose of the trial, the subjects were asked to fast overnight and abstain from smoking until a fasting blood sample was taken. Each subject then smoked two cigarettes in succession while talking to each other or reading magazines. A second specimen of blood was then withdrawn. After that, each subject was given 100 g. glucose in water, and further specimens of blood were collected at set intervals for blood glucose and serum insulin estimations. According to the original plan, subjects volunteered to abstain from smoking for 14 days after the first part of the experiment, but only three males and two females were able to do so. The above test was then repeated on these subjects. Glucose levels were estimated by the method of Folin and Wu, and serum insulin by immunoassay.

In the accompanying Table are shown the blood glucose and serum insulin levels in the fasting state, before and after smoking two cigarettes, and during the glucose tolerance test. The values found during the period of heavy smoking and after the cessation of smoking for 14 days may also be compared.

If excessive insulin response can be defined as insulin levels rising above 100 microunits per ml. serum during an oral glucose tolerance test[1] then subject No. 4 may not be considered to have hyperinsulinaemia. However, the marked drop in insulin response after she stopped smoking for 14 days indicates a relative hyperinsulinism during the period of heavy smoking. The view that hyperinsulinaemia is atherogenic is well documented.[2–5] The suggestion that it is the factor responsible for the liability of heavy smokers to develop atherosclerosis is an expansion of this theory.—I am, etc.,

Comparison of Blood Glucose and Serum Insulin Levels

Subject and Sex	Stage of Trial	Glucose (mg./100 ml. Blood)					Insulin (μu./ml. Serum)				
		Fasting		30 min.	60 min.	120 min.	Fasting		30 min.	60 min.	120 min.
		Before Smoking	After 2 Cigarettes				Before Smoking	After 2 Cigarettes			
1 M	30 cigarettes day ..	92	100	151	112	90	87	96	150	156	102
	Stopped 14 days ..	73	78	136	105	70	29	32	54	67	47
2 M	30–40 cigarettes day	85	90	127	103	84	52	58	112	109	61
	Stopped 14 days ..	66	83	112	100	80	35	43	63	57	35
3 F	25–30 cigarettes day	93	95	134	119	85	99	93	145	158	94
	Stopped 14 days ..	54	81	126	102	80	86	84	112	110	61
4 F	20–30 cigarettes day	90	95	145	120	87	33	30	95	84	60
	Stopped 14 days ..	73	108	141	114	80	8	11	26	22	13
5 M	50 cigarettes day ..	78	84	135	100	89	53	50	149	124	83
	Stopped 14 days ..	69	87	137	99	90	30	34	66	72	64

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3. Pelzer, N., and Haas, G. N., *ibid.* 1964, 1, 1111.
4. Vallance-Owen, J., *Lancet*, 1965, 2, 1177.
5. Wickham, T. A., Breckenridge, A., Robinson, A. H., Dudley, C. T., and Fraser, T. R., *Lancet*, 1966, 1, 1114.

Smoking and Atherosclerosis

SIR,—Your leader (26 March, p. 755) is a fair comment on the present uncertainty with regard to the effects of smoking on the coronary arteries. "On balance," you state, "the evidence is in favour of smoking being a cause, but it is still incomplete, and it would be greatly strengthened if the physiological and biochemical effects of smoking could be shown to contribute to the development of some parts of the disease process."

In a paper published earlier this year[1] it was shown how heavy smokers depend, in certain cases, on their nicotine consumption to maintain their blood sugar level within normal limits. When these people attempted to break with the habit they developed hypoglycaemic symptoms, and to counteract this they ate sweets in a quantity that was surprising even to themselves.

Recently it has been reported by several workers that refined carbohydrates increase the tendency of the blood platelets to stick to the arterial walls. If nicotine is interchangeable with the refined carbohydrates in maintaining the blood sugar on comfortable levels, is it not plausible that it can also cause an increased platelet stickiness in a similar way? To give this hypothesis a biochemical backing, it is known that nicotine exerts an antidiuretic effect due to its action on the hypothalamus. In a present, as yet unpublished, series of tests it was found that the excessive ingestion of glucose or sucrose by carbohydrate-deprived subjects may inhibit for more than four hours the diuresis that is normally expected following the drinking of a litre of water.—I am, etc.,

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Reference

1. Szanto, S., *J. Irish med. Assoc.*, 1966, 243, 22.

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Additional Considerations Regarding Coronary Blood Flow

Coronary blood flow, besides being influenced by the size of the inner lumen of the coronary vessel wall and its ability to dilate for the purpose of increasing flow of oxygenated blood when needed by heart muscle, is also dependent upon the viscosity of the blood (*16*). The concepts of fluid mechanics, such as laminar or turbulent flow, are well known. For any given aperture and pumping pressure, fluid flow will depend somewhat upon the physical characteristics of the fluid itself. It has been demonstrated in both cigarette smokers (*199*) and in patients with myocardial infarction that hemoconcentration occurs (*15, 137*), sometimes to a relatively small degree in terms of absolute changes in hematocrit, but the changes in viscosity are much greater than might have been predicted from consideration of hematocrit changes alone. At this point, other factors related to fluid mechanics also enter in, such as the quality and amount of lipids in the blood. Burch, et al. (*15*) have demonstrated that increased fatty acids increase the force necessary to "shear" the blood, thus contributing to a reduction in the capacity of the blood to flow in laminar fashion through a given aperture. When coronary arteries are impaired by partial obstruction of the inner lumen or by decreased distensibility, there may be a critical interaction with blood viscosity causing marked turbulence of flow and thus reducing further the potential for increasing coronary blood flow.

SUMMARY, CONCEPT AND CONCLUSION

Additional evidence has been presented which tends to confirm and extend the positive findings previously reported in the 1964 and 1967 reports.

1. Epidemiological studies show that "heavy" cigarette smoking is strongly associated with an increased risk of dying from coronary heart disease.

2. New data confirm and help to clarify the relationship between cigarette smoking and other "risk factors" in the development of coronary heart disease suggesting that both independent and interacting effects are involved.

3. Evidence indicates that cigarette smoking may accelerate the pathophysiological changes of pre-existent coronary heart disease and contribute to sudden cardiovascular death. This relationship helps to explain why stronger epidemiological correlations between cigarette smoking and coronary heart disease tend to be found in incidence studies rather than in prevalence studies where the population is under-represented for those people who have had fatal outcomes from coronary heart disease.

4. Present evidence continues to support the position that giving up cigarette smoking is beneficial to cardiovascular health.

5. Some progress is being made in the study of the interrelationships of selected psychological factors, smoking behavior, and the development of coronary heart disease.

Recent data provide a basis for the formulation of a theoretical concept by means of which it is possible to correlate the interaction of several known coronary heart disease risk factors with the physiological mechanisms by which cigarette smoking may affect the myocardium.

The epidemiological studies continue to indicate that "heavy" cigarette smoking is strongly associated with a fatal outcome from coronary heart disease. This fact may be accounted for by a mechanism whereby, in the presence of impaired coronary circulation due to coronary heart disease, cigarette smoking may "trigger" myocardial oxygen deficits of critical degree. One or more of the following mechanisms may be involved in this process:

1. The increase of myocardial wall tension and velocity of contraction, largely mediated through norepinephrine released in response to cigarette smoking, thereby increasing the myocardial demand for oxygen and other nutrients.

2. The relative reduction of nutrient capillary blood flow in the region of the myocardium distal to and dependent upon blood flow through a partially occluded coronary artery.

3. The impairment of oxygen dissociation from hemoglobin due to the formation of carboxyhemoglobin from carbon monoxide, thereby diminishing the availability of oxygen to the myocardium.

4. The reduction of the supply of oxygen available to the myocardium as a consequence of hypoxemia due to severely impaired pulmonary function from chronic obstructive bronchitis.

(106) McDonough, J. R., Hames, C. G., Garrison, G. E., Stulb, S. C., Lehtman, M. A., Hetherington, D. C. The relationship of hematocrit to cardiovascular states of health in the Negro and white population of Evans County, Georgia. Journal of Chronic Diseases 18(3): 243-257, March 1965.

(15) Burch, G. E., DePasquale, N. P. The hematocrit in patients with myocardial infarction. Journal of the American Medical Association 180(1): 63-70, April 7, 1962.

(137) Stables, D. P., Rubenstein, A. H., Metz, J., Levin, N. W. The possible role of hemoconcentration in the etiology of myocardial infarction. American Heart Journal 73(2): 155-160, February 1967.

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5. The impairment of coronary blood flow as a result of the increased blood viscosity associated with hyperlipemia or hemoconcentration.

6. The increase in platelet adhesiveness which might contribute to thrombus formation or coronary occlusion.

7. The predisposition to acute cardiac arrhythmias as a consequence of harmful neurogenic reflexes or catecholamine release.

8. The possible, although presently speculative, contributions to impairment of myocardial cellular respiration by cyanide ion.

Thus, the interaction of the factors which decrease oxygen supply to the myocardium and those which increase the myocardial demand for oxygen may play a major role in precipitating the fatal outcome in some individuals with coronary heart disease. On the other hand, it is possible that the same factors, in less severe clinical circumstances, could precipitate temporary coronary insufficiency or contribute to nonfatal myocardial infarctions or cardiac arrhythmias.

The pathophysiological factors associated with cigarette smoking may further interact with other known epidemiological risk factors associated with coronary heart disease such as high serum cholesterol and high blood pressure. Although not a "risk factor", unusually high physical stress may also create physiological demands for additional oxygen supply to the myocardium.

The finding that those who discontinue cigarette smoking have a lower risk of dying from coronary heart disease than those who continue to smoke might be accounted for by the potential reversibility of many of the pathophysiological effects of smoking on the cardiovascular system. It is reasonable to expect partial reversibility of factors that interfere with oxygen supply, such as the carbon monoxide effect, and the increased platelet adhesiveness, hyperlipemia, and hemoconcentration noted in cigarette smokers. Moreover, the increased myocardial oxygen requirements associated with the cigarette smoking-induced catecholamine response and neurogenic reflexes could be expected to be eliminated upon cessation of cigarette smoking. In some patients, the cardiopulmonary benefits of stopping smoking may reduce pulmonary hypertension.

An increased ability to predict future cardiovascular events in individual persons will depend upon more precise definition and measurement of the pathophysiologic factors associated with cigarette smoking and their correlation with information about the epidemiological risk factors.

Because of the increasing convergence of epidemiological and physiological findings relating cigarette smoking to coronary heart disease, it is concluded that cigarette smoking can contribute to the development of cardiovascular disease and particularly to death from coronary heart disease.

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"Trigger" Mechanisms for Cigarette Smoking. The impressive list of 8 mechanisms is not supported by sections in the 1968 document. It should be noted once more that for each mechanism, cigarette smoking was not used as the stimulus. In most instances, catecholamines, carbon monoxide and large doses of nicotine were used to elicit the "trigger" menchanism. The brief comments for each of the 8 in the list are as follows:

1. Increase in myocardial wall tension was elicited by doses of nicotine and cigarette smoke large enough to cause a rise in blood pressure in anesthetized dogs.
2. There are no observations that nicotine or catecholamines can reduce collateral blood flow.
3. The amount of carboxyhemoglobin in an ordinary smoker is about 5%.
4. Smokers have no impairment in pulmonary function unless they are suffering from chronic lung disease.
5. The lipidemia and hemoconcentration demonstrated acutely following smoking is not intense enough to impair blood flow.
6. The increase in platelet adhesiveness is not consistently found in most smokers. Furthermore, thrombosis has not been noted in animals receiving toxic doses of nicotine for an extended period of time.
7. The predisposition to acute cardiac arrhythmias was observed only in dogs exposed to huge quantities of cigarette smoke for 30 minutes.
8. The role of cyanide in cigarette smoking has not been proven.

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SMOKING AND CEREBROVASCULAR DISEASES

Many of the pathophysiological considerations noted in the above section may also pertain to the relationship of smoking and cerebrovascular disease.

A mortality study in Japan by Hirayama (*65*) reports findings different from those cited in the 1967 Report (*146*), in which smokers under age 75 had a mortality ratio of 1.40, or more, for stroke.

Hirayama found that deaths due to vascular lesions of the central nervous system, after age 40, were one-third less frequent among smokers than among nonsmokers. Several factors may account for these different findings. One is that the etiologic spectrum for stroke in Japan includes more hemorrhagic strokes than in the United States. Another is that the Japanese study included all stroke deaths over age 40, whereas the studies in the United States found the positive association between smoking and stroke mortality occurred under age 75 (*54*).

In a study reported by Kuhn (*93*), 20 habitual smokers refrained from smoking for one-half day and baseline retrograde brachiocerebral angiograms were taken; then they smoked one cigarette, inhaled deeply, and had repeat angiograms. Only those over 60 years of age failed to have significant acceleration of flow in cerebral precapillary vessels and markedly increased vessel counts as in carbon dioxide inhalation experiments.

As in coronary heart disease, it may be that smoking has different effects depending upon the degree of underlying arteriosclerotic disease present. Among patients with stroke, many have arteriosclerotic heart disease and a significant number die of myocardial infarcts (*104*).

The rate of oxygen uptake in the brain is very high, being approximately 5 cc. oxygen/100 g. brain/min. (*104*). As discussed in the cardiovascular section, if carbon monoxide causes a shift to the left in the oxygen hemoglobin dissociation curve, it would make less oxygen available to the brain tissue. Those people with an arteriosclerotic cerebrovasculature who cannot increase their cerebral blood flow in response to smoking may therefore more easily develop a state of relative cerebral hypoxia; a situation which could be a factor in the etiology of stroke.

(93) KUHN, R. A. Mode of action of tobacco smoke inhalation upon the cerebral circulation. Annals of the New York Academy of Sciences 142 (Article 1): 67–71, March 15, 1967.

(104) MEYER, J. S. Personal communication. 1968.

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The Health Consequences of SMOKING

1969 SUPPLEMENT TO THE

1967 Public Health Service Review

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Public Health Service

CHAPTER 1

Smoking and Cardiovascular Diseases

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Summary

Coronary heart disease (CHD) among men in the Western world is an epidemic which cuts short the lives of many in their prime productive years. The evidence linking smoking and CHD has been reported not only from studies in the United States, but also from such diverse areas as West Germany, the U.S.S.R., France, Israel, Italy, and the British Isles.

The 1968 Supplement (27) stated:

> Because of the increasing convergence of epidemiological and physiological findings relating cigarette smoking to coronary heart disease, it is concluded that cigarette smoking can contribute to the development of cardiovascular disease and particularly to death from coronary heart disease.

The convergence of autopsy data and experimental data presented in this and previous reports suggests that cigarette smoking promotes atherosclerosis, including that of the coronary arteries. The results of physiological research and the findings of diminished risk of CHD in those who have stopped smoking indicate that there is also a more immediate mechanism operative. The mechanisms which might be responsible for the promotion of myocardial infarction and fatal cardiac arrhythmias by cigarette smoking were extensively reviewed in the 1968 Supplement (27). Briefly stated, nutrient supply to the myocardium in general and, perhaps more importantly, to focal ischemic areas of the myocardium may be seriously compromised by a combination of effects caused by smoking, and the deprived myocardium may become infarcted or develop an arrhythmia. These effects include diminution of blood flow through atherosclerotic coronary vessels and diminution of available oxygen for tissue use resulting from the binding of carbon monoxide to hemoglobin in the place of oxygen and possibly, although presently speculative, the poisoning of respiratory enzymes by hydrogen cyanide.

Cigarette smoking has been shown to be an important risk factor in the development of CHD. It is important both by itself and in the presence of other significant risk factors. In combination with certain other risk factors, the joint effects appear to be even greater than those accounted for by those risk factors independently.

(27) U.S. Public Health Service. The Health Consequences of Smoking. 1968 Supplement to the 1967 Public Health Service Review. Washington, U.S. Department of Health, Education, and Welfare, Public Health Service Publication No. 1696. 1968. 117 pp.

Epidemiological Studies

Hammond, et al. (11) have presented new data on mortality from CHD, stroke, and nonsyphilitic aortic aneurysm among more than 800,000 men and women who were between the ages of 40 and 70 in 1959. The authors were attempting to evaluate the significance of multiple factors (sex, age, diabetes, high blood pressure, body weight, change in weight, exercise, cigarette smoking, sleep, and nervous tension) in the variations in death rates from these three diseases. It should be noted that this information consisted of self-reports obtained by questionnaire and were not obtained from medical examination. Causes of death were based on death certificate reports.

As illustrated in table 1, coronary heart disease death rates and mortality ratios increased with increased cigarette smoking for men in all age groups and for women under the age of 70. Although the mortality ratios were higher in the younger age groups, the differences in death rates between nonsmokers and heavy smokers became progressively higher with increasing age. Although CHD rates were highest for those who were 10 percent or more above the average weight for their height-age-sex group, and for those who reported having high blood pressure, the trend is clear that the effect of smoking persists and is appreciable, even when these other factors are held constant (table 2).

(11) Hammond, E. C., Garfinkel, L. Coronary heart disease, stroke, and aortic aneurysm. Factors in the etiology. Archives of Environmental Health 19(2): 167-182, August 1969.

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TABLE 1.—*Death rates and mortality ratios for coronary heart disease and stroke, by amount of cigarette smoking, sex, and age*

Sex and age	Coronary heart disease					Stroke				
	Never smoked cigarettes regularly	Regularly smoked cigarettes				Never smoked cigarettes regularly	Regularly smoked cigarettes			
		Number smoked daily					Number smoked daily			
		1-9	10-19	20-39	40 or more		1-9	10-19	20-39	40 or more
DEATH RATES										
Males:										
40-49 years	65	103	176	226	375	14	30	[2]16	31	33
50-59 years	257	409	544	616	715	40	78	60	81	96
60-69 years	650	961	1,194	1,241	1,104	168	219	242	272	259
70-79 years	1,730	1,970	2,431	2,573	2,543	650	817	808	792	[2]445
Females:										
40-49 years	13	17	27	47	[2]43	10	15	26	29	[2]67
50-59 years	50	68	149	153	220	27	34	73	72	[2]95
60-69 years	268	279	479	558	[2]542	110	139	238	201	—
70-79 years	979	760	963	1,283	—	497	404	[2]276	622	—
MORTALITY RATIOS[1]										
Males:										
40-49 years	1.00	1.60	2.50	3.76	6.51	1.00	2.79	[2]1.16	2.21	1.64
50-59 years	1.00	1.59	2.13	2.40	2.79	1.00	1.95	1.48	2.03	2.40
60-69 years	1.00	1.48	1.82	1.91	1.70	1.00	1.30	1.44	1.62	1.72
70-79 years	1.00	1.14	1.41	1.49	1.47	1.00	.85	.92	1.22	[2].68
Females:										
40-49 years	1.00	1.31	2.08	3.62	[2]3.31	1.00	1.50	2.60	2.90	[2]5.70
50-59 years	1.00	1.13	2.37	2.64	3.73	1.00	1.26	2.70	2.67	[2]3.52
60-69 years	1.00	1.04	1.73	2.08	[2]2.02	1.00	1.26	2.15	1.83	----
70-79 years	1.00	.78	.98	1.27	----	1.00	.83	[2].47	1.25	----

[1] The mortality ratio is the observed rate divided by the expected rate.
[2] Rates based upon only 5 to 9 deaths.

SOURCE: Hammond, E. C., et al. (11).

TABLE 2.—*Coronary heart disease death rates for men and women classified by smoking habits, age, blood pressure, and relative weight*

Extent of cigarette smoking and age	No high blood pressure, by relative weight					High blood pressure, by relative weight				
	Total	Less than 90	90-109	110-119	120 and over	Total	Less than 90	90-109	110-119	120 and over
MEN										
None or slight:										
40-49 years	52	[2]27	45	64	128	204	...	195	[2]210	.....
50-59 years	226	140	218	253	370	630	[2]656	611	643	699
60-69 years	603	542	573	701	763	1,503	1,777	1,293	1,660	1,955
70-79 years	1,611	1,467	1,555	1,843	1,858	2,733	3,342	2,568	2,631	3,100
Intermediate:										
40-49 years	118	106	104	141	245	349	[2]354	266	[2]256	.....
50-59 years	373	352	363	435	538	876	1,424	656	1,182	995
60-69 years	558	814	850	944	973	1,876	1,913	1,999	1,447	1,710
70-79 years	1,973	2,237	1,776	1,953	2,901	3,220	3,700	3,172	2,213	6,451
20 or more:										6
40-49 years	222	123	215	309	278	647	697	550	765	68[2]
50-59 years	530	422	536	656	641	1,137	1,143	1,153	923	1,41
60-69 years	1,047	978	1,019	1,249	1,307	1,955	2,160	1,913	1,744	2,075
70-79 years	2,256	2,346	2,205	2,151	2,846	4,123	5,141	4,205	[2]3,692	.....
WOMEN										
None or slight:										
40-49 years	8	[2]6	7	---	22	63	---	83	-----	76
50-59 years	41	39	32	64	68	181	100	142	157	229
60-69 years	201	153	191	265	323	469	400	475	462	459
70-79 years	776	832	779	657	756	1,338	1,313	1,217	1,449	1,626
Intermediate:										
40-49 years	15	17	12	---	---	96	---	[2]76	-----	-----
50-59 years	78	69	70	123	[2]73	281	361	281	[2]233	[2]198
60-69 years	294	337	344	422	---	730	773	743	845	[2]454
70-79 years	607	736	551	---	---	1,101	[2]1,854	1,014	-----	-----
20 or more:										
40-49 years	36	25	35	[2]42	[2]72	144	---	195	-----	-----
50-59 years	120	118	128	---	[2]135	358	[2]293	291	[2]664	[2]706
60-69 years	467	341	502	[2]637	---	911	[2]795	1,100	-----	-----
70-79 years	844	[2]866	[2]963	---	---	2,453	---	[2]3,743	-----	-----

[2] Rates based upon only 5 to 9 deaths.

SOURCE: Hammond, E. C., et al. (11).

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Hammond, et al. also studied CHD mortality among men who were ex-smokers of cigarettes. The death rates from CHD were lower among the ex-smokers than among those still smoking at the beginning of the study, the size of the difference being larger the longer they had been off smoking (table 3). Some people stop smoking because of illness or symptoms and these people would be expected to have higher death rates than those who stop for other reasons. Early deaths among those with preexisting disease may account, at least in part, for the high death rates from CHD among ex-smokers in the early years of abstention.

Mortality ratios for stroke were higher among cigarette smokers with the exception of those over 70 years of age. Male ex-cigarette smokers had mortality ratios for stroke approximately equal to those of nonsmokers.

A clear increase in mortality from nonsyphilitic aortic aneurysms with increasing cigarette smoking among men aged 50–69 is seen in table 4. The mortality ratio for heavy smokers was 8.00.

Hammond, et al. found that death rates from the three diseases varied considerably with relative weight, amount of exercise, amount of cigarette smoking, and hours of sleep per night. Subjects who were obese, took little or no exercise, smoked many cigarettes a day, or slept 9 or more hours per night had high death rates. Those with a combination of these factors have especially high death rates from the three diseases.

TABLE 3.—*Observed and expected number of deaths and mortality ratios for ex-cigarette smokers with a history of smoking only cigarettes, by number of years since last cigarette smoking and for current cigarette smokers, coronary heart disease and stroke; compared to persons who never smoked regularly, in men aged 40–79*

Type of smoker	Coronary heart disease			Stroke		
	Observed	Expected	Ratio	Observed	Expected	Ratio
Ex-cigarette smokers (former smokers of 1-19 cigarettes a day):						
Stopped:						
Less than 1 year	29	17.9	1.62	------	------	------
1-4 years	57	46.6	1.22	------	------	------
5-9 years	55	43.7	1.26	------	------	------
10-19 years	52	34.1	.96	------	------	------
20 or more years	70	64.7	1.08	------	------	------
Total	263	226.9	1.16	87	86.9	1.00
Current cigarette smokers	1,063	557.5	1.90	207	134.5	1.54
Never smoked regularly	1,841	1,841.0	1.00	501	501.0	1.00
Ex-cigarette smokers (former smokers of 20 or more cigarettes a day):						
Stopped:						
Less than 1 year	62	38.6	1.61	------	------	------
1-4 years	154	101.9	1.51	------	------	------
5-9 years	135	116.5	1.16	------	------	------
10-19 years	133	106.1	1.25	------	------	------
20 or more years	80	78.4	1.05	------	------	------
Total	364	437.7	1.25	94	101.1	0.93
Current cigarette smokers	2,822	1,104.7	2.55	440	234.7	1.87
Never smoked regularly	1,841	1,841.0	1.00	501	501.0	1.00

Source: Hammond, E. C., et al. (11).

TABLE 4.—*Aortic aneurysm death rates and mortality ratios for men aged 50–69, classified by cigarette smoking habits*

[Rates per 1,000 population]

Measure	Never smoked regularly	Current smokers, by daily cigarette consumption			
		5-9	10-19	20-39	40 or more
Death rate	13	34	50	59	104
Mortality ratio	1.00	2.62	3.85	4.54	8.00

Source: Hammond, E. C., et al. (11).

They also found that death rates from CHD and stroke were lower in ex-cigarette smokers than in men who were currently smoking cigarettes at the time they enrolled in the study. The death rates of male ex-cigarette smokers who had not smoked for 10 to 20 years were no higher or only slightly higher than the death rates of men who had never smoked regularly. Death rates from the three diseases were lowest among subjects without a history of diabetes or high blood pressure who were not obese, took at least moderate exercise, never smoked regularly and slept 6 to 8 hours per night. Nevertheless, even these subjects had substantial death rates from CHD, stroke and nonsyphilitic aortic aneurysm.

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Source: https://www.industrydocuments.ucsf.edu/docs/rrlk0000

Stamler (*21*) has analyzed 10-year mortality data on a total cohort of men, aged 40–59 in 1958, who were employees of the Chicago Peoples Gas Light and Coke Co. Of 1,465 men examined, 1525 were found initially to be free of definite CHD and have been followed without systematic intervention. Higher overall death rates were found among the smokers in the study. Table 5 shows the death rates from CHD and from all causes for men with various risk factors.

Recent papers by Thorne, et al. (*23*) and by Paffenbarger, et al. (*19*) report further results of studies of CHD among former college students. College health records and other college records were reviewed to ascertain the presence or absence of factors under consideration. Cases were identified from death certificates in the study of fatal CHD (*19*) and from questionnaires and physical examinations in the study of nonfatal CHD (*23*). Matched controls were obtained for each case. In both nonfatal and fatal CHD, significantly more smokers were found among the cases than among the controls. Combinations of risk factors resulted in greater CHD morbidity and mortality ratios than did single factors. Figure 1 shows the morbidity ratios for combinations of pairs of risk factors in nonfatal CHD and table 6 shows mortality ratios for combinations of risk factors in fatal CHD.

(21) Stamler, J. Personal Communication. 1969.

(23) Thorne, M. C., Wing, A. L., Paffenbarger, R. S., Jr. Chronic illness in former college students. VII. Early precursors of nonfatal coronary disease. American Journal of Epidemiology 87(3) : 329–339. May 1.

(19) Paffenbarger, R. S., Jr., Wing, A. L. Characteristics in college years disposing to fatal coronary heart disease in later life. (In press) American Journal of Epidemiology : 1969.

TABLE 5.—*10-year mortality rates for sudden death, coronary heart disease, stroke, cardiovascular-renal, and all causes combined among men aged 40–59, classified according to cigarette smoking, cholesterol, and blood pressure*

[People's Gas Light Co. study, 1956–65. Men originally free of coronary heart disease and followed without systematic intervention.]

1958 risk factor status—cigarette smoking (10 or more a day), hypercholesterolemia, hypertension[1]	10-year mortality									
	Sudden death			All CHD		Stroke		All CVR		All causes
	Number of men in cohort	Number of deaths	Death rate[2]	Number of deaths	Death rate	Number of deaths	Death rate	Number of deaths	Death rate	Number of deaths	Death rate
No risk factor	254	0	0	1	3.9	2	8.0	4	15.9	23	93.6
Hypercholesterolemia or hypertension only—1 factor	218	4	18.4	15	69.1	6	28.6	20	72.6	37	186.2
Cigarette smoking only (1 or more a day)—1 factor	492	6	12.6	18	37.1	5	11.5	20	44.9	64	157.7
Hypercholesterolemia and hypertension only—2 factors	69	1	6.9	3	20.6	1	6.7	1	7.3	6	121.9
Cigarette smoking (10 or more a day) and hypercholesterolemia or cigarette smoking and hypertension—2 factors	288	11	32.2	17	47.1	6	15.9	26	86.4	53	168.9
Cigarette smoking (10 or more a day), hypercholesterolemia, hypertension—all 3	57	2	25.1	6	70.6	2	25.4	6	101.6	17	223.8
Total	[3]1,373	23	16.9	61	38.2	22	14.9	81	56.0	102	113.1

[1] Risk factors include: Serum cholesterol 250 or more mg/dl; diastolic blood pressure 90 or more mm. Hg; 10 or more cigarettes/day.

[2] All rates are age-adjusted by 6-year age groups to the U.S. male population, 1960. All rates per thousand.

[3] Smoking data were not obtained for 4 of the 1,525 men.

Source: Stamler, J. (*21*).

TABLE 6.—*Estimated coronary heart disease death ratios in a 17–51 year follow-up among former college students, classified according to combined presence (+) or absence (−) of each of three specified risk factors, and by age*

Risk factor			Age (years) at death from coronary heart disease			
Cigarettes, 1 or more per day	Systolic B.P., 140 or more mm. Hg	Parental history, before age 60	Total 39–59 years	39–44 years	45–54 years	55–59 years
+	+	+	4.3	[1](1.9)	5.7	[1](4.5)
+	−	+	1.8	2.3	1.6	[1](2.0)
+	+	−	4.2	2.9	4.5	5.6
−	+	+	1.9	2.9	1.6	1.3
+	−	−	1.7	2.2	1.9	1.3
−	+	−	1.3	1.2	1.2	1.4
−	−	+	1.1	1.4	1.4	.8
−	−	−	1.0	1.0	1.0	1.0

[1] Numbers in parentheses indicate expected number coronary heart disease deaths less than 5.

Source: Paffenbarger, R. S., et al. (*19*).

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Source: https://www.industrydocuments.ucsf.edu/docs/rnk0000

In a study of participants in the Health Insurance Plan of New York, Weinblatt, et al. (29) reported that cigarette smoking males who developed angina pectoris were more likely to develop infarction than were nonsmoking anginal patients, but there were not enough cases to draw definite conclusions.

Weinblatt, et al. (30) also reported that the prognosis after the development of a myocardial infarction appears to be independent of smoking status prior to the infarct. In the absence of data indicating which patients stop smoking and how stopping smoking is related to the severity of myocardial damage, one cannot evaluate the effect of smoking on prognosis. If the persons who stop smoking tend to include the most debilitated, the effect of continued smoking on prognosis would be underestimated.

In a prospective study of over 3,000 men, Jenkins, et al. (14) reported that the incidence of CHD in men aged 39–49 was three times higher among the cigarette smokers than among the nonsmokers (table 7). The incidence of CHD increased with increased daily cigarette consumption. For men aged 50–59, the relationship between cigarette smoking and CHD was found to be significant only for the heavy

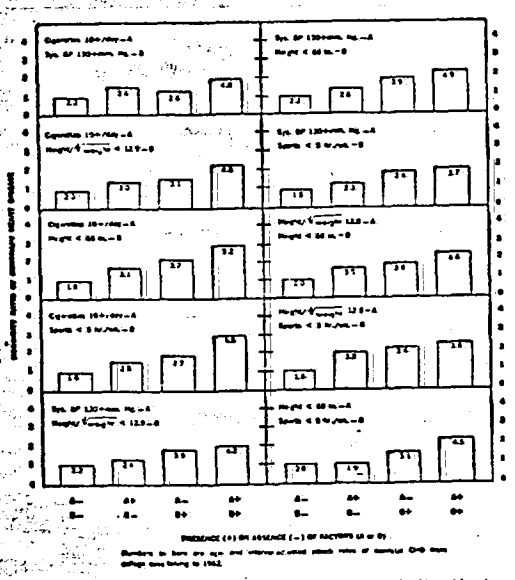

FIGURE 1.—Morbidity ratios of coronary heart disease for paired combinations of factors in college.

SOURCE: Thorne, M.C., et al. (25).

smokers (table 8). Former cigarette smokers also had significantly higher CHD incidence rates, but no data are given on length of time since stopping smoking, or reasons for stopping. Pipe and cigar smokers did not have higher CHD incidence rates. After controlling for other risk factors such as lipid levels, diastolic blood pressure, and body build, the authors found that the association between cigarette smoking and CHD remained (tables 9, 10). The relationship between smoking and CHD was stronger among those men who exhibited behavior type A than those exhibiting behavior type B (tables 11, 12). Behavior type A is characterized by enhanced competitiveness, drive, aggressiveness, hostility, and an excessive sense of time urgency. Behavior type B indicates an absence of these characteristics. Analysis of the data on behavior and cigarette smoking showed that both factors have effects on the CHD rate. Again, these associations were stronger in the younger age group.

(29) WEINBLATT, E., FRANK, C. W., SHAPIRO, S., SAGER, R. V. Prognostic factors in angina pectoris—a prospective study. Journal of Chronic Diseases 21(4): 231–245, July 1968.

(30) WEINBLATT, E., SHAPIRO, S., FRANK, C. W., SAGER, R. V. Prognosis of men after first myocardial infarction: Mortality and first recurrence in relation to selected parameters. American Journal of Public Health and the Nation's Health 58(8): 1329–1347, August 1968.

(14) JENKINS, C. D., ROSENMAN, R. H., ZYZANSKI, S. J. Cigarette smoking. Its relationship to coronary heart disease and related risk factors in the Western Collaborative Group Study. Circulation 38(6): 1140–1147, December 1968.

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Prognosis of Myocardial Infarction. The article by (30) Weinblatt et al. is being criticized for absence of data indicating which patients stop smoking. The article did not mention exsmokers. Only smokers and nonsmokers are reported. Anyway, the basis for statement that prognosis is independent of smoking states is as follows:

Table 4—Early mortality among men following first MI in relation to physical activity level and smoking habits at time of MI, age-adjusted per cent dead within one month

Characteristic at time of MI	No.	% dead (age-adj.)
Physical activity level*		
Least active	261	43.6
Other classified	523	25.0
Intermediate	280	28.6
Most active	243	20.5
Least active, no limitation of activity prior to MI	200	40.4
Men without prior CHD		
Least active	186	38.8
Other classified	426	22.6
Men without elevated blood pressure		
Least active	143	36.1
Other classified	365	19.5
Men with neither prior CHD nor elevated blood pressure		
Least active	108	30.0
Other classified	299	17.6
Men without other CV disease		
Least active	211	37.4
Other classified	466	22.7
Smoking habits		
All cigarette smokers†	487	32.6
Two or more packs daily	177	27.1
Less than two packs daily	304	35.2
Pipe and/or cigar smokers	110	27.5
Nonsmokers	237	38.0

*Description of the construction of the physical activity classes used in the HIP study has been published (J. Chron. Dis. 18:527, 1965). In general, the three levels are defined in terms of specified combinations of four classes of job-connected activity and four classes of off-job activity. Each of the job-connected and off-job categories is defined as a specified range of accumulated scores of the weights assigned to specific questionnaire items.

†Includes six cigarette smokers, amount unknown.

Cigarette smoking—especially heavy cigarette smoking—has been reported as associated with an increased risk for incidence of first MI among men in the HIP study population,[6] but no influence of smoking on early mortality could be demonstrated from the preliminary data.[2] This finding is confirmed by the data shown for the full cohort in Table 4.

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TABLE 7.—*Annual incidence rates of coronary heart disease for men 30–49 years of age, classified by smoking history and by current practices as to cigarette smoking*

[Age as of the beginning of the 4½ year period of observation]

Morbidity status	Total subjects		Smoking history								Current cigarette smoking by number per day							
			Never smoked		Pipe and cigar only		Former cigarette		Current cigarette		None		1–15		16–25		26 or more	
	Number	Rate[1]	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate
Total number at risk	2,873	.....	340	.....	465	.....	229	.....	1,004	.....	1,121	.....	211	.....	434	.....	422	.....
Total number CHD cases	83	8.2	7	[2] 2.9	3	1.6	10	[2] 9.3	63	[2] 15.9	20	[2] 3.7	5	4.3	13	[2] 8.3	20	[2] 10.6
All myocardial infarction	52	5.1	4	1.7	3	1.6	10	9.3	35	7.3	17	3.1	4	4.2	13	6.7	15	9.3
Symptomatic	34	3.7	1	.4	2	1.1	8	7.4	27	5.6	11	2.0	4	4.2	11	5.6	12	6.3
Unrecognized	16	1.4	3	1.2	1	.5	2	1.9	8	1.7	6	1.1	0	0	2	1.0	6	3.1
Fatal	2	.2	0	0	0	0	1	.9	0	1.7	1	.2	0	0	0	2.6	3	1.6
Angina pectoris only	11	1.1	3	1.2	0	0	0	0	8	1.7	3	.6	1	1.0	0	2.6	2	1.1

[1] Annual rate per 1,000 men at risk.

[2] These distributions of cases for various smoking categories are significantly different from chance at P=0.01.

[3] Difference in CHD frequency between this group and those who never smoked cigarettes (col. 1 and 2 combined) is significant at P=0.01 by chi square test corrected for continuity.

[4] Difference in CHD frequency between this group and current noncigarette smokers is significant at P=0.01.

Source: Jenkin, C. D., et al. (11).

TABLE 8.—*Annual incidence rates of coronary heart disease for men 50–59 years of age, classified by smoking history and by current practices as to cigarette smoking*

[Age as of the beginning of the 4½ year period of observation]

Morbidity status	Total subjects		Smoking history								Current cigarette smoking by number per day							
			Never smoked		Pipe and cigar only		Former cigarette		Current cigarette		None		1–15		16–25		26 or more	
	Number	Rate[1]	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate
Total number at risk	934	.....	132	.....	161	.....	137	.....	444	.....	453	.....	109	.....	167	.....	165	.....
Total number CHD cases	79	16.9	9	[2] 11.0	11	13.2	8	14.6	41	20.6	23	[2] 12.3	6	12.2	16	21.3	[2] 19	21.6
All myocardial infarction	62	12.5	6	7.3	8	11.0	6	8.1	33	16.3	19	8.7	5	10.2	15	20.0	13	17.6
Symptomatic	35	8.4	4	4.9	4	5.5	4	5.5	23	11.6	12	5.5	4	8.2	11	14.6	8	10.8
Unrecognized	17	4.1	2	2.4	4	5.5	1	1.6	10	5.0	7	3.2	1	2.0	4	5.3	5	6.7
Fatal	14	3.4	0	0	3	4.1	3	4.9	8	4.0	6	2.8	2	4.1	1	1.3	2	2.7
Angina pectoris only	18	4.3	3	3.7	3	4.1	4	6.5	8	4.0	10	4.6	1	2.0	1	1.3	6	8.1

[1] Annual rate per 1,000 men at risk.

[2] These distributions of cases for various smoking categories could occur 0.10 of the time by chance, hence are not significant at P=0.05.

[3] Difference in CHD frequency between this group and current noncigarette smokers is significant at P=0.01.

Source: Jenkins, C. D., et al. (11).

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TABLE 9.—*Annual incidence rates of new coronary heart disease, by smoking habits, adjusted for age and seriatim, for specified other risk factors*

[Rates are annual incidence per 1,000 men, aged 30 to 49 years at entry into study]

Specified other risk factors	Never smoked	Former cigarette smokers	Pipe and cigar only	Daily cigarette consumption			p.[1]
				1-15	16-25	26 or more	
Cholesterol	33	83	22	49	89	100	0.005
Beta-alpha ratio	31	81	15	49	91	102	.001
Lipalbumin	31	85	16	51	89	102	.002
Systolic BP	31	81	15	49	95	100	.001
Diastolic BP	29	89	16	49	95	104	.001
Ponderal index	29	81	16	49	95	107	.001
Physical activity	29	83	15	47	93	104	.001
Amount of exercise	29	81	15	49	93	104	.001
Income level	29	91	16	49	93	104	.001
All of the above	26	83	20	81	89	86	.007
Triglycerides	31	88	20	40	83	104	.002

[1] Level of significance of F-ratio for analysis of covariance.

Source: Jenkins, C. D., et al. (*14*).

TABLE 10.—*Annual incidence rates of new coronary heart disease, by smoking habits, adjusted for age and seriatim, for specified other risk factors*

[Rates are annual incidence per 1,000 men, aged 50 to 59 years at entry into study]

Specified other risk factors	Never smoked	Former cigarette smokers	Pipe and cigar only	Daily cigarette consumption			p.[1]
				1-15	16-25	26 or more	
Cholesterol	116	142	153	115	211	304	0.156
Beta/alpha ratio	107	142	144	130	213	302	.127
Lipalbumin	109	140	151	122	218	302	.135
Systolic BP	118	127	144	129	211	296	.136
Diastolic BP	109	127	135	127	230	273	.066
Ponderal index	107	131	149	122	222	269	.054
Physical activity	113	142	149	115	213	249	.216
Amount of exercise	113	144	151	113	211	255	.263
Income level	113	138	147	120	220	258	.156
All of the above	113	118	138	140	213	258	.158
Triglycerides	113	147	141	90	195	260	.121

[1] Level of significance of F-ratio for analysis of covariance.

Source: Jenkins, C. D., et al. (*14*).

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TABLE 11.—*Incidence of new coronary heart disease, by smoking category and behavior type, for men aged 30–49*

[Rates are age-adjusted annual incidence per 1,000 men]

Behavior type	Never smoked		Former cigarette smokers		Current and former pipe and cigar only		Daily cigarette consumption						Total	
							1-15		16-25		26 or more			
	Rates	Cases	Rates	Cases	Rates	Cases	Rates	Cases	Rates	Cases	Rates	Cases	Rates	Cases
A	6.3	5	13.8	7	1.3	1	1.6	1	16.8	15	16.9	16	9.3	45
B	1.3	2	3.1	3	2.2	2	7.3	4	3.1	3	4.9	4	3.3	18
Total	2.9	7	9.1	10	1.8	3	4.9	5	8.3	18	10.4	20	6.2	63

Source: Jenkins, C. D., et al. (*14*).

TABLE 12.—*Incidence of new coronary heart disease, by smoking category and behavior type, for men aged 50–59*

[Rates are age-adjusted annual incidence per 1,000 men]

Behavior type	Never smoked		Former cigarette smokers		Current and former pipe and cigar only		Daily cigarette consumption						Total	
							1-15		16-25		26 or more			
	Rates	Cases	Rates	Cases	Rates	Cases	Rates	Cases	Rates	Cases	Rates	Cases	Rates	Cases
A	12.4	6	18.6	8	21.8	8	18.4	8	21.5	9	30.0	14	20.4	48
B	10.0	4	8.1	1	8.4	3	6.7	1	21.1	7	19.1	8	12.0	21
Total	11.1	9	16.2	9	14.9	11	11.6	6	21.3	16	26.0	19	13.8	70

Source: Jenkins, C. D., et al. (*14*).

Source: https://www.industrydocuments.ucsf.edu/docs/rrlk0000

Epidemiological studies linking smoking and CHD have been carried out in various countries. In a retrospective study in Dublin, of 400 patients under the age of 65 who experienced myocardial infarction, Mulcahy, et al. (*18*) observed a definite association between smoking and the development of the disease.

A prospective epidemiological study of risk factors of CHD, in an Israeli population, indicates that smoking is associated with a higher risk of CHD (*17*).

In a retrospective study of 503 male patients with myocardial infarction and 714 age-matched controls in Munich, Schimmler, et al. (*22*) report that cigarette smoking plays a significant role as a risk factor.

A recent paper by Cederlof, et al. (*5*) employs the twin-study method on a population of American twins, using a similar approach to that previously employed in a Swedish twin population. The purpose is to compare the contribution of genetic and environmental influences to the development of angina pectoris. The authors imply that their study indicates a more important role for genetic factors than for smoking. However, this study can be criticized on several grounds. The authors based their detection of angina pectoris on the results of a self-administered questionnaire designed to elicit a history of chest pain of presumable cardiac origin; previous studies in Swedish twins have shown a low rate of clinical confirmation of heart disease in those classified positive by questionnaire. No data are available on the health and smoking habits of 58 percent of the original group or the 41 percent of the "eligible twin pairs" who were nonrespondents. The authors' definition of a present smoker includes persons who have stopped smoking cigarettes for up to 3 years and thus includes persons who in other studies have been classified as ex-smokers. This definition of a cigarette smoker might contribute to an underestimation of the immediate effect of current cigarette smoking, since an unstated number of recent ex-smokers are included in the same category as current cigarette smokers.

The relationship between cigarette smoking and the development of angina pectoris has not been clarified. However, Aronow, et al. (*1*) have shown that smoking one cigarette before exercising reduces the energy expenditure required for patients with classical angina pectoris to develop chest pain while exercising on a bicycle ergometer.

Atherosclerosis

A review of autopsy studies by Strong and Auerbach, suggesting that cigarette smoking has a chronic effect leading to advanced degrees of atherogenesis, was presented in the Health Consequences of Smoking, 1967 (*26*). Further studies have recently been published in this area.

Sackett, et al. (*21*) have demonstrated a clear dose-relationship between cigarette smoking and the severity of aortic atherosclerosis at autopsy. Their study of 1,019 consecutive autopsies, on patients who had been interviewed about their smoking habits prior to death, showed a significant increase in the severity of aortic atherosclerosis with increasing use of cigarettes, measured both by intensity and by duration of smoking.

An autopsy study from Russia by Avtandilov, et al. (*3*) demonstrated a significantly greater degree of atherosclerosis in the coronary arteries of smokers than in those of nonsmokers.

Viel, et al. (*28*) have reported on the severity of coronary atherosclerosis at autopsy of 1,150 men and 290 women who died violent deaths in Chile. Information on smoking habits was available on 566 men. The authors report no relationship between atherosclerotic lesions and the use of tobacco. The degree of atherosclerosis was expressed as the percentage of the surface of the intima of the left anterior descending coronary artery covered by fatty streaks and fibrous plaques. An examination of the data presented in graphic form indicates that the moderate and heavy smokers appear to show consistently higher percentages of diseased areas than the nonsmokers. But the statement of the authors implies that these differences were not statistically significant when subjected to an analysis of variance.

A study by Astrup was reviewed in the 1968 Report (*27*). This study showed that in rabbits on a high cholesterol diet, chronic carbon monoxide exposure has a marked atherogenic effect.

(*18*) Mulcahy, R., Hickey, N., Maurer, B. Coronary heart disease, a study of risk factors in 400 patients under 60 years. Geriatrics 24(1): 106-114, January 1969.

(*17*) Medalie, J. H., Kahn, H. A., Groen, J. J., Neufeld, H. N., Riss, E. The prevalence of ischemic heart disease in relation to selected variables. Israel Journal of Medical Sciences 4(4): 789-800, July-August 1968.

(*22*) Schimmler, W., Nefv, C., Schimert, G. Risikofaktoren und Herzinfarkt. Eine retrospektive Studies. Münchener Medizinische Wochenschrift 110(27): 1585-1594, July 5, 1968.

(*5*) Cederlof, R., Friberg, L., Hrubec, Z. Cardiovascular and respiratory symptoms in relation to tobacco smoking. A study on American twins. Archives of Environmental Health 18(6): 934-940, June 1969.

(*1*) Aronow, W. S., Kaplan, M. A., Jacob, D. Tobacco: A precipitating factor in angina pectoris. Annals of Internal Medicine 69(3): 529-536, September 1968.

(*26*) U.S. Public Health Service. The Health Consequences of Smoking. A Public Health Service Review: 1967. Washington, U.S. Department of Health, Education, and Welfare, Public Health Service Publication No. 1696, 1967. 199 pp.

(*21*) Sackett, D. L., Gibson, R. W., Bross, I. D. J., Pickren, J. W. Relation between aortic atherosclerosis and the use of cigarettes and alcohol. An autopsy study. New England Journal of Medicine 279(26): 1413-1420, December 26, 1968.

(*3*) Avtandilov, G. G., Kolenova, V. I., Ponomarenko, O. V. Kureniye tabaka i stepen' ateroskleroticheskogo porazheniya koronarnykh arteriy serutsa i aorty. (Tobacco smoking and the degree of atherosclerotic lesions of coronary arteries of the heart and aorta.) Kardiologiya 5(1): 30-34, January-February 1965.

(*28*) Viel, B., Donoso, S., Salcedo, D. Coronary atherosclerosis in persons dying violently. Archives of Internal Medicine 122(2): 97-103, August 1968.

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Source: https://www.industrydocuments.ucsf.edu/docs/rrlk0000

Cigarette Smoking and Angina. The report of (1) Aronow et al. is based on 10 selected patients who have been trained on an ergometer. The shortening of exercise time before pain appeared following smoking was not seen on 8 occassions out of 40 times in 10 patients. There were no nonsmoking controls to show their variability for comparison and there was no indication of incidence of reactors to the test in a group of unselected anginal patients.

The calculation of tension-time index was calibrated in dogs. The modification introduced has not been checked in man to prove that the index represents myocardial oxygen. The manner of reasoning by the authors is reproduced as follows:

Discussion

The results of the present study indicate a significant relationship between cigarette smoking and the appearance, with less provocation, of angina pectoris in patients who have known coronary artery disease.

Well-known effects of smoking are increases in both blood pressure and heart rate (7). Indeed, all of the subjects in these studies developed increases in these parameters after smoking. The increase in heart rate and blood pressure is based upon the known increase in catecholamine discharge from the adrenal medulla and from chromaffin tissue in the heart that occurs during smoking (9–11). Nicotine is also known to act on chemoreceptors in the carotid and aortic bodies, reflexly causing acceleration of the heart rate and an increase in blood pressure (12). In addition, low concentrations of nicotine can stimulate sympathetic ganglion cells.

The product of blood pressure and heart rate has been found to be a good index for the oxygen cost of cardiac hemodynamic activity (13). Sarnoff and coworkers (14) have found the primary hemodynamic determinant of oxygen consumption of the heart to be the total tension developed by the myocardium (heart rate times the area under the systolic portion of the aortic pressure curve). Robinson (15) states, "... the precipitation of angina could be consistently related to the level reached by the product of heart rate and systolic blood pressure (corrected when necessary for changes in ejection time)." Using this index, it can be readily seen that smoking increases the oxygen consumption of the heart.

Patients with coronary heart disease increase the myocardial demand for oxygen when they exercise. The present study indicates that this increase is even greater when the exercise is preceded by smoking. In such instances, patients with coronary disease cannot meet the increased demands for myocardial oxygen. Therefore, there is a decreased amount of time between the performance of exercise and the onset of angina after smoking.

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Source: https://www.industrydocuments.ucsf.edu/docs/rrik0000

Kjeldsen, et al. (15) compared the vascular pathology in rabbits fed a high cholesterol diet and maintained in an hypoxic atmosphere (10 percent oxygen) with that in rabbits exposed only to the high cholesterol diet. The authors demonstrated that hypoxia leads to an increase in the degree of plaque formation in the coronary arteries and in the amount of visible aortic atheromatosis, as well as to an increase in the aortic content of cholesterol and triglycerides. In addition, the hearts of the hypoxic animals showed marked perivascular xanthomatosis, often infiltrating the surrounding myocardium. In summarizing this experiment and their previous findings of increased atheromatosis in hypercholesterolemic rabbits subjected to high carboxyhemoglobin (COHb) levels, the authors (2) state that tissue hypoxia seems to be an important factor in initiating these lesions, regardless of the manner in which the hypoxia is produced. Although the COHb levels in the rabbits and the degree of hypoxia were much higher than that experienced by human smokers, these results suggest a mechanism by which smoking might contribute to atherosclerosis.

Hass, et al. (12), extending studies reviewed in the 1968 Report (27), have demonstrated that the administration of injections of nicotine to hypercholesterolemic rabbits who are also given vitamin D enhances the peripheral atheromatous calcific arterial disease which is produced by the combination of hypercholesterolemia and vitamin D administration. The addition of nicotine to the regimen also resulted in the frequent occurrence of thromboarteritis in the distal calcified arteries of cardiac and skeletal muscle, and of the smooth muscle of the gastrointestinal tract. The nicotine effect was reproduced by substituting appropriate dosages of adrenalin for nicotine and abolished by adrenalectomy.

Lellouch, et al. (16) have reported that the administration of a mono-amine oxidase (MAO) inhibitor to rabbits on a regimen of daily nicotine injections significantly reduced the number of animals who developed fibrotic lesions of the aorta in response to nicotine. Further work is in progress to elucidate the mechanism of the MAO effect.

Evidence presented in this and previous reports suggests that cigarette smoking promotes atherosclerosis.

Thrombus Formation and Blood Flow

Hess, et al. (13) discovered aggregations of platelets, erythrocytes fibrin, detached epithelial cells, and some as yet unidentified cells or the aortic and carotid walls of rabbits subjected to cigarette smoke

The discovery of a plasma factor which increases the *in vitro* synthesis of fibrinogen by human liver biopsies has been reported by Pilgeram, et al. (20) in older patients who have recovered from myocardial infarction. This factor has been tentatively identified as free fatty acid (FFA). The authors state that the association between FFA and fibrinogen synthesis may provide the link between hyperlipemia and clotting. Cigarette smoking causes an increase in FFA through its stimulation of catecholamine release.

Several recent studies have begun to elucidate the role which changes in blood viscosity and certain features of the microcirculation might play in the development of atherosclerosis and coronary heart disease.

Dintenfass (7) has suggested that myocardial infarction and coronary thrombosis may be the result of a number of factors, separate or interrelated, all leading to a high viscosity of the blood. These factors may affect the migration and adhesion of platelets, the volume of plasma, and the rigidity of the red blood cell. Phenomena leading to high blood viscosity may occur in focal areas leading to occlusion of small vessels, resultant ischemia, and an infraction of either subclinical or catastrophic proportions, depending on the location and number of vessels involved. Dintenfass also believes that an increase in blood viscosity precedes the clinical manifestations of the high blood viscosity syndrome and that the increased blood viscosity seen in post myocardial infarct patients is a reflection of the etiology rather than the effect of the disease.

Local hypoxia leading to an increase in the rigidity of the blood cell might be produced by cigarette smoking through the increase in COHb. Platelet adhesiveness is increased by smoking, probably secondary to the release of catecholamines (27).

In a study of 50 white males with myocardial infarcts and 40 controls, Stables, et al. (23) found that the patients with myocardial infarct had a mean hematocrit level significantly higher than that of the controls. Studies of blood volume indicated that a reduction in plasma volume rather than an increase in red cell mass among the myocardial infarct patients accounted for the elevated hematocrit.

(15) Kjeldsen, K., Wanstrup, J., Astrup, P. Enhancing influence of arterial hypoxia on the development of atheromatosis in cholesterol-fed rabbits. Journal of Atherosclerosis Research 8(5): 835–845, 1968.

(2) Astrup, P., Kjeldsen, K., Wanstrup, J. Enhancing influence of carbon monoxide on the development of atheromatosis in cholesterol-fed rabbits. Journal of Atherosclerosis Research 7: 343–354, 1967.

(12) Hass, G., Henson, D., Langerholm, W., Hemmens, A. Prevention of nicotine induction of atherocalcific thromboarteritis in rabbits. Circulation 38 (4, Supplement 6): 8, October 1968.

(16) Lellouch, J., Jacotot, B., Anguera, G., Grosgogeat, J., Beaumont, J.-A. Action chronique de la nicotine sur l'intima aortique du lapin. Influence d'un inhibiteur de la mono-amine oxydase (I.M.A.O.) Journal of Atherosclerosis Research 8(1): 137–142, January/February 1968.

(13) Hess, H., Frost, H. Rauchen und arterielle Verschlusskrankheiten. Fortschritte der Medizin 86(19): 841–843, October 10, 1968.

(20) Pilgeram, L. O., Pickart, L. R. Control of fibrinogen biosynthesis: The role of free fatty acid. Journal of Atherosclerosis Research 8: 155–1[illegible] 1968.

(7) Dintenfass, L. Blood rheology in pathogenesis of the coronary heart diseases. American Heart Journal 77(1): 139–147, January 1969.

(23) Stables, D. P., Rubenstein, A. H., Metz, J., Levin, N. W. The possible role of hemoconcentration in the etiology of myocardial infarction. American Heart Journal 73(2): 155–159, February 1967.

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Source: https://www.industrydocuments.ucsf.edu/docs/rrlk0000

Vitamins and atherosclerosis. The introduction of Vitamin D into the investigation of atherosclerosis raises the question of the role of other vitamins. Spittle subsequently wrote a letter to the Editor of Lancet (April 8, 1972), recalling the long association between Vitamin C and atherosclerosis.

ATHEROSCLEROSIS AND VITAMIN C

SIR,—Dr. Morin (March 11, p. 594) feels that I may be overoptimistic in attributing[9] the rise in serum-cholesterol after vitamin C in patients with atherosclerosis to arterial mobilisation, and that perhaps there is a potential danger in the administration of large doses of vitamin C.

It is of interest that my first observations were made with fruits and vegetables, before I realised that the active agent was vitamin C. Even with these much smaller quantities of vitamin C, I was able to produce the same effects. It was with healthy older people on a vitamin-C-rich diet that I first saw the rise in level which led me to investigate the patients. It is true that many of the patients were having other therapy as well as vitamin C, but this cannot be said of the healthy subjects.

There are some features which add very strong supportive evidence to my conclusion that vitamin C is the only factor involved in atherosclerosis.

Carnivorous animals do not have atherosclerosis, and they synthesise their own vitamin C. It is possible to give them atherosclerosis without giving a deliberately atherogenic diet. This has happened in the Philadelphia Zoological Gardens.[10] Lesions were noticed about five years after the introduction of improved diets for the animals. This is the only instance that I am aware of which compares with the fate of the human who embarks on a "westernised" diet, and it shows that animals behave in the same way as humans when the balance between vitamin C and fats is disturbed.

There is a seasonal variation in deaths from myocardial infarction,[11] which coincides with our maximum and minimum consumption of vitamin C.

Two standard measures are advocated for all coronary patients in the interests of preventing a further attack; to give up smoking and to lose weight. Both these measures increase the available vitamin C—the second by its abundance in a low-calorie diet.

Recently, I did a necropsy on a man who had been in a mental hospital since the age of 12 years. He had been having vitamin supplements since admission. He died at the age of 62 years, from drowning. His arteries were clean.

I should like to emphasise again that Sokoloff[12] in his series had no recurrence of myocardial or cerebral infarction with vitamin-C treatment in 2½ years, and he states that 50 of his 60 patients were a lot better. This, surely, is consistent with an arterial "decoke".

We should start a large-scale trial of this substance in patients with atherosclerosis.

Pinderfields General Hospital,
Aberford Road,
Wakefield, Yorkshire.

CONSTANCE R. SPITTLE.

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Fibrinogen Synthesis. The paragraph is written as though (2) Pilgeram and Pickart associated their Results with cigarette smoking. The association was added by somebody else. There is no mention of cigarette smoking in Pilgeram and Pickart's article. Note that the transposition of results is increasing by one step as follows: cigarette smoking ⟶ release of epinephrine ⟶ elevation of FFA ⟶ fibrinogen synthesis ⟶ clotting ⟶ atherosclerosis.

DISCUSSION

A role for FFA in the turnover of fibrinogen could have been predicted by the correlation of a number of earlier studies. For example, incorporation of glycine into fibrinogen is enhanced by epinephrine[5,9]. However, epinephrine is well known to mobilize FFA[10]. ACTH has been reported to raise the plasma content of fibrinogen[11,12]. ACTH administration has been shown to induce elevation in plasma FFA and to induce thrombosis[13]. Chronic stress syndromes have been associated with elevations in plasma fibrinogen[14-16]. However stress has also been found to induce an output or increase of epinephrine, cholesterol, and FFA[17-20]. Stress has also been associated with myocardial infarction or coronary thrombosis[21]. Cortisone, depending upon dosage, induces an increase in fibrinogen[22] or a decrease[23]. Cortisone also restores the mobilization of FFA in adrenalectomized animals exposed to trauma[10], etc.

Correlation of a number of reports also suggests a role for FFA in the formation of fibrin or fibrinogen-fibrin intermediates. Saturated long chain fatty acids shorten the clotting time and accelerate thrombus formation[24-27], activate Hageman factor[28], aggregate platelets[29], activate plasma thromboplastin antecedent[30], and induce thrombosis *in vivo*[27]. Although the clot promoting effect of FFA has been confirmed by a number of investigators, a failure of the fatty acid salt to accelerate the clotting of native plasma *in vitro*, *i.e.*, plasma that had not been decalcified, has been reported[30]. On the basis of this study, the authors concluded that it seemed doubtful that FFA are of importance in the development of intravascular thrombi. However, this con-

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clusion requires reexamination in view of the study which showed that thrombi were induced *in vivo* by the infusion of fatty acid salts[27]. In these latter experiments the fatty acid salt entered into native plasma and still induced thrombi. From these considerations and from the data reported in this paper, it would appear warranted to suggest that FFA not only control the rate of synthesis or turnover of the soluble precursor of the clot forming protein, fibrin, but also play a significant role in determining the rate of formation of fibrin or precursors thereof. The enhanced rate of turnover of fibrinogen[4] is indicative of both an increase in the rate of biosynthesis and an increase in utilization. Study of the turnover rate does not in itself show the nature of the enhanced pathways of utilization. It is therefore pertinent to consider those reports which bear upon the nature of the pathway(s) of utilization of fibrinogen which are enhanced by FFA. The correlation of an enhanced turnover rate of fibrinogen with coronary thrombosis[4] and with changes in blood clotting indices, which are indicative of enhanced generation of thrombin, is suggestive of an increase in the formation of fibrin or fibrinogen–fibrin intermediates. For example, enhanced generation of plasma thromboplastin[31,32] and a deficiency in plasma antithromboplastin[33] are found in thrombotic complications. An enhanced level of antithrombin[34], possibly a protective feed-back mechanism against thrombin, is found in coronary thrombosis. An increased concentration of plasma fibrinogen is also found in coronary thrombosis[1,4,31]. This increase has been shown to correlate with the enhanced rate of biosynthesis and utilization[4]. Our recent study, which shows that thrombin induces, *in vivo*, a significant increase, up to 1.9-fold, in the rate of biosynthesis of fibrinogen[35] suggests that the enhanced rate of turnover reflects conversion of fibrinogen to fibrin. These correlations are made with an awareness that the platelets play an important role in the formation of thrombi. However, it has been recently shown that platelets will not clump unless fibrinogen is present[36]. The role of fibrinogen, fibrin, and thrombin in the clumping and utilization of platelets was recently reviewed[37]. The fact that thrombin not only enhances the turnover of platelets but also the turnover of fibrinogen[4] combined with the observations that both the turnover of platelets[38] and the turnover of fibrinogen[4] are enhanced in coronary artery disease suggests that conversion to fibrin is a significant pathway in the enhanced turnover of fibrinogen.

A control by FFA over the metabolism of fibrinogen may have implications with respect to unifying the two theories on atherogenesis which are based either on disturbed fat metabolism or on blood clotting. The intravascular deposition of fibrin-platelet thrombi has been implicated as a cause of arteriosclerosis since the time of Vos Rokitansky[39]. Numerous recent histological investigations show that thrombi on the vessel surfaces give rise to intimal thickening and eventually arteriosclerosis[40–47]. Recently, injections of thrombin into the areas of the intima and the media were shown to produce atheroma[48].

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Carbon Monoxide

Several reviews of the pathophysiology of exposure to carbon monoxide (CO) have appeared recently. These are pertinent to the discussion of the relationship of smoking to health, since cigarette smoke contains amounts of CO sufficient to cause a COHb level of 5 to 10 percent in the smoker, depending on the amount smoked and degree of inhalation (*2, 10*).

Bartlett (*4*) has pointed out that because the absorption of CO from the ambient environment is dependent upon the concentration of CO in the environment as contrasted to that in the blood, smokers with a COHb level of 5 percent will not absorb CO from inspired air unless the concentration of CO in the air exceeds 30 parts per million. However, he also states that because the excretion of CO between cigarettes will be lower in CO polluted air, the smoker will have a higher long-term average COHb level in a polluted environment. Patients with heart disease may be particularly susceptible to the hypoxic burden caused by the presence of COHb.

Goldsmith, et al. (*10*) have stated that for the U.S. urban population, cigarette smoking is probably the most important cause of increased COHb above the endogenous level produced by heme catabolism, followed by automobile exhaust, occupational sources, and home heating and cooking devices, in that order.

Although Dinman (*6*) minimizes the importance of the effect of CO levels of 5 to 10 percent on the myocardium, he states that a shortcoming in his approach is that focal areas of myocardial ischemia are not reflected in the determination of oxygen saturation made from samples of blood taken from the coronary sinus. Such areas of ischemia might be important in initiating fatal arrhythmias. Levels of COHb which decrease further the oxygen supply to the ischemic myocardium might be readily provided by cigarette smoking.

Eliot, et al. (*3*) have reported effects of cigarette smoking on the oxygen affinity of hemaglobin independent of the presence of CO. Their results suggest that cigarette smoking may have both acute and chronic effects on oxygen affinity which differ in direction. The authors caution, however, that the *in vivo* oxygen affinity of hemoglobin may be different from that implied by the static equilibrium data. Further research is in progress.

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(10) Goldsmith, J. R., Landaw, S. A. Carbon monoxide and human health. Science 162(3860): 1352–1359, December 20, 1968.

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(6) Dinman, B. D. Pathophysiologic determinants of community air quality standards for carbon monoxide. Journal of Occupational Medicine 10(9): 446–463, September 1968.

(3) Eliot, R. S., Steiff, R., Salhany, J. M., Mizukami, H. Personal Communication. April 1969.

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The Health Consequences of Smoking

A Report of the Surgeon General: 1971

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service

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INTRODUCTION

Coronary Heart Disease (CHD) cuts short the lives of many men in the Western World in their prime productive years. More Americans die from heart disease than from any other disease. In 1967, in this country, a total of 345,154 men and 227,999 women were classified as dying of arteriosclerotic heart disease (ASHD) (*196*), a category which consists largely of what is commonly called CHD. During the years from 1950 to 1967, the age-adjusted death rate from ASHD increased 15.1 percent (*196, 197*).

Besides the many deaths attributed to CHD, much morbidity results from this disease. The National Health Examination Survey of 1960–1962 estimated that 3.1 million American adults, ages 18 to 79, had definite CHD and 2.4 million had suspect CHD, together representing about 5 percent of the population. It was further estimated that of Americans under age 65, almost 1.8 million had definite CHD and 1.6 million had suspect CHD (*195*).

There are several manifestations of CHD, all related in part to the basic process of severe atherosclerosis, a disease of arteries in which fatty materials (lipids) accumulate in the form of plaques in the walls of medium and large arteries. This process, as it occurs in the coronary arteries, leads to stiffening of the wall and narrowing of the lumen which, when severe, result in a diminution in the blood supply to the cardiac muscle. Angina pectoris, a major manifestation of CHD, results from diminution in blood supply relative to the needs of the myocardium. If the blood supply to a portion of the myocardium is completely obstructed, due for example to the formation of a thrombus at the site of atherosclerotic narrowing, necrosis or death of a portion of heart muscle may occur. This occurrence is known as a myocardial infarction. In many cases, a disturbance of cardiac rhythm occurs at the time of thrombosis, and the patient may die immediately. It is estimated that approximately 25 percent of patients suffering coronary artery occlusion die within the first three hours following the occlusion (table 1) (*88*). Not infrequently, sudden death occurs in patients with severe coronary atherosclerosis but without a demonstrable arterial occlusion. In these cases, it is thought that the meager blood flow to a portion of the myocardium becomes so diminished with respect to cardiac needs as to lead to a fatal arrhythmia, as well as to, perhaps, a myocardial infarction.

(196) U.S. PUBLIC HEALTH SERVICE. NATIONAL CENTER FOR HE... STATISTICS. Vital Statistics of the United States—1967, Vo... Mortality, Part A. Washington, U.S. Department of Health, ... tion and Welfare, Public Health Service Publication. 1969.

(197) U.S. PUBLIC HEALTH SERVICE. NATIONAL CENTER FOR HEA... STATISTICS. Vital Statistics Rates in the United States 19... Washington, U.S. Department of Health, Education and We... Public Health Service Publication No. 1677, 1968. 881 pp.

(195) U.S. PUBLIC HEALTH SERVICE. NATIONAL CENTER FOR HEA... STATISTICS. Vital and Health Statistics. Data from the N... Health Survey. Coronary Heart Disease in Adults—United S... 1960–1962. Washington, U.S. Department of Health, Educatio... Welfare, National Center for Health Statistics Series 11, N... September 1965. 46 pp.

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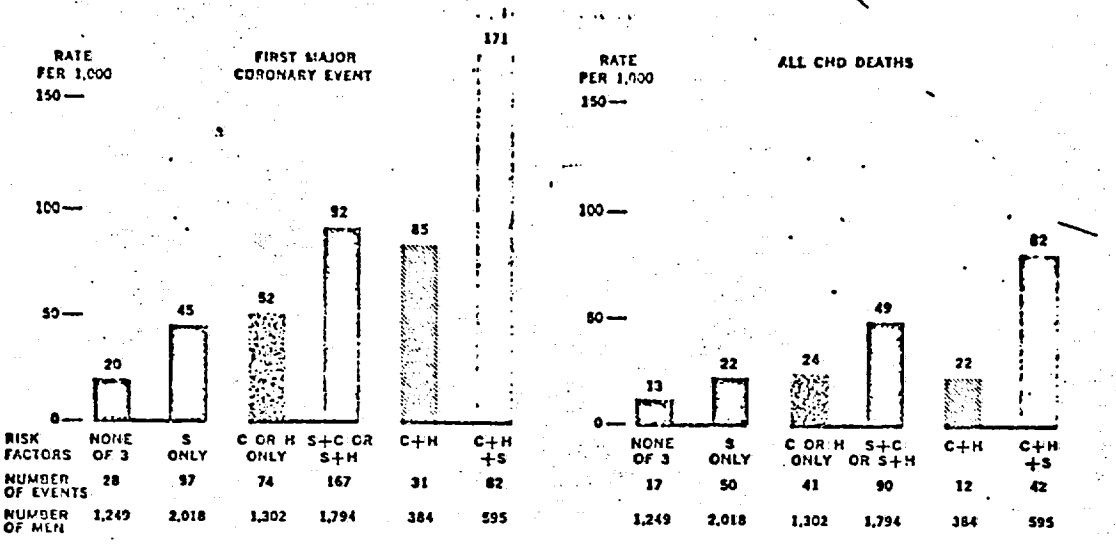

National Cooperative Pooling Project; smoking status at entry and 10-year age-adjusted rates per 1,000 men for first major coronary event (incling nonfatal MI, fatal MI, and sudden death due to CHD) and any coronary death. U.S. white males age 30–59 at entry. All rates age-adjusted by 10-year age groups to the U.S. white male population 1960. Graphs present rates for noncigarette vs. cigarette smokers at entry with simultaneous control of blood pressure and serum cholesterol level. For this latter analysis, the following cutting points were used:

(a) Cigarette smoking S —any use at entry
(b) Serum cholesterol C — 250 mg./dl.
(c) Diastolic blood pressure H — 93 mm. Hg.

SOURCE: Inter-Society Commission for Heart Disease Resources. National Cooperative Pooling Project Data (88).

FIGURE 1—National Cooperative Pooling Project; smoking status at entry and 10-year age-adjusted rates per 1,000 men for first major coronary event (includes nonfatal MI, fatal MI, and sudden death due to CHD) and any coronary death. U.S. white males age 30–59 at entry. All rates age-adjusted by 10 year age groups to the U.S. white male population 1960. Graphs present rates for noncigarette vs. cigarette smokers at entry with simultaneous control of blood pressure and serum cholesterol level. For this latter analysis, the following cutting points were used:

(a) Cigarette smoking—S–any use at entry
(b) Serum cholesterol—C–≧250 mg./dl.
(c) Diastolic blood pressure—H–≧90 mm. Hg.

SOURCE: Inter-Society Commission for Heart Disease Resources. National Cooperative Pooling Project Data (*88*).

TABLE 1.—*Sudden death and acute mortality with first major coronary episodes*

Author, year, country, reference	Number and type of population	Data collection	Event	Number of events	Proportion per 1,000 events (as calculated on the basis of age-adjusted rates)	Comment
Pooling Project, American Heart Association, 1970, U.S.A. (*88*).	7,824 males males 30–59 years of age at entry. Ten-year experience.	Medical examination and follow-up.	All first major coronary episodes, nonfatal and fatal.	601	1,000.0	Data from the Pooling Project, Council on Epidemiology, American Heart Association, a national cooperative project for pooling data from the Albany civil servant, Chicago Peoples Gas Co., Chicago Western Electric Co., Framingham Community, Los Angeles civil servant, Minneapolis-St. Paul business men, and other prospective epidemiologic studies of adult cardiovascular disease in the United States.
			Sudden death (death within 3 hours of onset of acute illness).	123	246.8	
			All acute deaths with first episodes.	165	329.3	

SOURCE: Inter-Society Commission for Heart Disease Resources (*88*). Representative references include: (*54, 96, 148, 177*) and others listed as 6a–6k in Inter-Society Commission for Heart Disease Resources report.

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(88) INTER-SOCIETY COMMISSION FOR HEART DISEASE RESOURCES. Atherosclerosis Study Group and Epidemiology Study Group. Primary prevention of the atherosclerotic diseases. Circulation 42(6): A–54–A–95, December 1970.

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(177) STAMLER, J., BERKSON, D. M., LEVINSON, M., LINDBERG, H. A., MOJONNIER, L., MILLER, W. A., HALL, Y., ANDELMAN, S. L. Coronary artery disease. Status of preventive efforts. Archives of Environmental Health 13(3): 322–335, September 1966.

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TABLE 2.—*Coronary heart disease mortality ratios related to smoking—prospective studies*

(Actual number of deaths shown in parentheses)[1]

[SM = Smokers NS = Nonsmokers]

Author, year, country, reference	Number and type of population	Data collection	Follow-up (years)	Number of deaths	Cigarettes/day	Cigars, pipes	Age variation	Comments
Hammond and Horn, 1958, U.S.A. (77, 78).	187,783 white males in 8 states 50–63 years of age.	Questionnaire and follow-up of death certificate.	3½	8,297	NS .....1.00 (709) All smokers .1.70 (3361) <10 .....1.29 (192) 10–20 ....1.89 (864) 20–40 ....2.20 (604) >40 .....2.41 (118)	*Cigars* NS..1.00 SM..1.28 (420) *Pipes* NS..1.00 SM..1.03 (312)	*50–54* *55–59* *60–64* *65–69* NS .....1.00 (90) 1.00 (142) 1.00 (294) 1.00 (278) All smokers .1.93 (765) 1.85 (962) 1.46 (721) 1.41 (715) <10 .....1.38 (35) 1.38 (50) 1.17 (62) 1.27 (68) 10–20 .....2.00 (213) 2.04 (258) 1.51 (235) 1.58 (159) >20 .....2.51 (203) 2.47 (193) 1.92 (129) 1.56 (73)	[1] ($p<0.001$)
Doyle et al., 1964, U.S.A. (64).	2,282 males, Framingham, 30–62 years of age. 1,913 males, Albany, 39–55 years of age.	Detailed medical examination and follow-up.	10 8	93	NS .....1.00 (20) All smokers .2.40 (73) <20 .....2.00 (17) 20 .....1.70 (20) >20 .....2.50 (36)			Data apply only to males aged 40–49 and free of CHD at entry. NS include pipe, cigar and ex-smokers.
Doll and Hill, 1964, Great Britain (50).	Approximately 41,000 male British physicians.	Questionnaire and follow-up of death certificate.	10	1,376	NS .....1.00 All smokers .1.35 1–14 ....1.29 15–24 ....1.27 >25 .....1.43		*35–44* *45–64* *65–84* NS .....1.00 1.00 1.00 1–14 .....2.73 1.40 1.71 15–24 .....4.45 1.73 1.27 >25 .....1.86 1.92 1.88	
Strobel and Gsell 1965 Switzerland (180).	3,749 male Swiss physicians.	Questionnaire and follow-up of death certificate.	9	162	NS .....1.00 1–20 .....1.48 >20 .....1.76	NS..1.00 SM..1.45		
Best, 1966 Canada (24).	Approximately 78,000 male Canadian veterans.	Questionnaire and follow-up of death certificate.	6	2,000	NS .....1.00 All smokers .1.60 (1350) <10 .....1.55 (337) 10–20 .....1.58 (766) >20 .....1.78 (277)	*Cigars* NS..1.00 SM..0.95 (16) *Pipes* NS..1.00 SM..0.96 (95)	*50–69* *50–69* *70 and over* <10 .....0.87 (18) 1.56 (220) 1.71 (99) 10–20 .....1.45 (115) 1.67 (557) 1.29 (94) >20 .....1.85 (65) 1.76 (184) 1.73 (25)	
Kahn 1966 U.S.A. (89).	U.S. male veterans 2,265,674 person years.	Questionnaire and follow-up of death certificate.	8½	10,830	NS .....1.00 (2397) All smokers .1.74 (4150) 1–9 .....1.39 (439) 10–20 .....1.78 (2102) 21–39 .....1.81 (1292) >39 .....2.00 (4266)	*Cigars* NS..1.00 SM..1.04 (623) *Pipes* NS..1.00 SM..1.08 (336)		
Hirayama, 1967, Japan (84).	265,118 Japanese adults over age 40.	Trained interviewers and follow-up of death certificate.	1	61	NS .....1.00 (17) 1–24 .....1.13 (69) >25 .....1.00 (8)			Preliminary report.
Kannel et al., 1968, U.S.A. (94).	5,127 males and females age 30–59.	Medical examination and follow-up.	12	62	NS .....1.00 (27) SM>20 ....2.20 (25)			[1] ($p<0.05$)

[1] Unless otherwise specified, disparities between the total number of deaths and the sum of the individual smoking categories are due to the exclusion of either occasional, miscellaneous, mixed, or ex-smokers.

[1] "p" values specified only for those provided by authors.

(77) HAMMOND, E. C., HORN, D. Smoking and death rates—report on forty-four months of follow-up of 187,783 men. I. Total mortality. Journal of the American Medical Association 166 (10): 1159–1172, March 8, 1958.

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(50) DOLL, R., HILL, A. B. Mortality in relation to smoking: 10 years' observations of British doctors. (Part I) British Medical Journal 1(5395): 1399–1410, May 30, 1964.

(180) STROBEL, M., GSELL, O. Mortalität in Beziehung zum Tabakrauchen: 9 Jahre Beobachtungen bei Ärzten in der Schweiz. (Mortality in relation to tobacco smoking. Nine years of observation in Swiss doctors.) Helvetica Medica Acta 32(6): 547–592, December 1965.

(24) BEST, E. W. R. A Canadian Study of Smoking and Health. Ottawa, Department of National Health and Welfare, 1966. 133 pp.

(84) HIRAYAMA, T. Smoking in relation to the death rates of 265,118 men and women in Japan. National Cancer Center, Research Institute. Tokyo, September 1967. 14 pp.

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TABLE 2.—*Coronary heart disease mortality ratios related to smoking—prospective studies (cont.)*

(Actual number of deaths shown in parentheses)[1]

[SM = Smokers NS = Nonsmokers]

Author, year, country, reference	Number and type of population	Data collection	Follow-up (years)	Number of deaths	Cigarettes/day	Cigars, pipes	Age variation	Comments
Hammond and Garfinkel, 1969, U.S.A. (76).	355,534 males 445,875 females age 40–79 at entry.	Questionnaire and follow-up of death certificate.	6	14,819	*Males* *Females* NS .....1.00 1.00 1–9 .....1.27 0.84 10–19 .....1.60 1.22 20–30 .....1.75 1.52 >40 .....1.77 0.61		*Males* *40–49* *50–59* *60–69* *70–79* NS .....1.00 1.00 1.00 1.00 1–9 .....1.60 1.59 1.48 1.14 10–19 .....2.59 2.13 1.82 1.41 20–30 .....3.76 2.40 1.91 1.49 >40 .....5.61 2.79 1.79 1.47 *Females* NS .....1.00 1.00 1.00 1.00 1–9 .....1.31 1.15 1.06 0.76 10–19 .....2.05 2.37 1.79 0.98 20–30 .....3.52 2.68 2.08 1.27 >40 .....†3.31 3.73 †2.02 —	†Based on 5–9 deaths.
Paffenbarger and Wing 1969 U.S.A. (146)	50,000 male former students.	Baseline interview and examination and follow-up by death certificate.	17–51	1,145 matched with 2,292 controls	NS .....1.00 SM .....1.50 (385) (p<0.01)		*30–44* *45–54* *55–69* NS .....1.00 1.00 1.00 (p<0.01) SM 1.80 (88) 1.60 (163) 1.20 (134)	
Paffenbarger et al., 1970, U.S.A. (144).	3,263 male longshoremen 35–64 years of age.	Initial multiphasic screening and follow-up of death certificate.	16	291	NS and <20 1.00 (137) SM >20 ....2.08 (154) (p<0.01)			
Taylor et al., 1970, U.S.A. (183).	8,571 male railroad employees 40–59 years of age at entry.	Interviews and regular follow-up examination.	5	48	NS .....1.00 (4) <20 .....1.97 (20) >20 .....3.60 (22)			Data apply only to those free of CHD at entry.
Weir and Dunn, 1970, U.S.A. (205).	68,153 California male workers 35–64 years of age at entry.	Questionnaire and follow-up of death certificate.	5–8	1,718	NS .....1.00 All smokers .1.60 ±10 .....1.39 ±20 .....1.67 >30 .....1.74		*35–44* *45–54* *55–64* *65–69* NS .....1.00 1.00 1.00 1.00 ±10 .....4.22 2.05 1.41 1.17 ±20 .....6.14 3.17 1.64 1.26 ±30 .....8.57 3.33 1.66 1.36 >40 .....7.93 3.16 1.42 1.42 All 6.24 2.96 1.56 1.24	NS includes pipes and cigars. SM includes ex-smokers.
Pooling Project, American Heart Association, 1970, U.S.A. (58).	7,427 white males 30–59 years of age at entry.	Medical examination and follow-up.	10	239	NS .....1.00 (27) <10 .....1.66 (34) 20 .....1.70 (56) >20 .....3.00 (66)	1.00 (27) 1.20 (24)		

[1] Unless otherwise specified, disparities between the total number of deaths and the sum of the individual smoking categories are due to the exclusion of either occasional, miscell[illegible]

(146) PAFFENBARGER, R. S., JR., WING, A. L. Chronic disease in former college students. X. The effects of single and multiple characteristics on risk of fatal coronary heart disease. American Journal of Epidemiology 90(6): 527–535, December 1969.

(144) PAFFENBARGER, R. S., JR., LAUGHLIN, M. E., GIMA, A. S., BLACK, R. A. Work activity of longshoremen as related to death from coronary heart disease and stroke. New England Journal of Medicine 282(20): 1109–1114, May 14, 1970.

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Longshoremen Study. Another interpretation to the report of (144) Paffenbarger et al. is raised in the Letter to the Editor by Chretien (N Engl J Med 283: 100, 1970). The answer by Paffenbarger is also reproduced below.

OCCUPATIONAL PRESELECTION

To the Editor: The recent study of longshoremen by Paffenbarger et al. (NEJM 282:1109-1113, 1970) attributes the higher coronary rate in sedentary workers than in cargo handlers to differences in work activity, even after the influences of blood pressure and cigarette smoking are taken into account.

Similar studies in Great Britain among bus drivers[1] and postal workers[2] have uncovered a confounding factor — men who are initially taller and heavier for a given height select the more sedentary jobs.

Do the authors have any such information about the longshoremen?

JANE HENKEL CHRETIEN, M.D.
Student
Harvard School of Public Health
Boston, Mass.

1. Morris JN, Heady JA, Raffle PAB: Physique of London busmen — epidemiology of uniforms. Lancet 2:569-570, 1956
2. Oliver RM: Constitutional differences between men recruited for driving and non-driving occupations. Brit J Indust Med 26:289-293, 1969

The above letter was referred to the authors of the article in question, one of whom offers the following reply:

To the Editor: Essentially all longshoremen entered their industry as cargo handlers, performing strenuous, work-day tasks in the ship's hold, at dockside and in the warehouse for a minimum of five years. Men who shifted to physically less demanding jobs, which carry higher pay scales and greater authority, had compiled an adequate work record and seniority status. They shifted after an average of ab 13 years as cargo handlers.

Table 1. Mean Body Height and Weight Levels of Longshoremen According to Physical Activity of Work and Age at Initial Examination.

Age (Yr) in 1951	More Active Workers	Less Active Workers
	Mean Height (in)	Mean Weight (in)
35-44	68.9	68.9
45-54	68.1	68.3
55-64	67.6	67.7
Average	68.3	68.3
	Mean Weight (lb)	Mean Weight (lb)
35-44	180.6	185.6
45-54	178.3	179.8
55-64	177.9	180.2
Average	179.0	181.4
Adjusted for age & height*	179.1	181.2

Table 1, which gives a cross-section of the study popu tion in 1951, shows no difference in height between m and less active workers, with the less active averaging g (2 lb) heavier in weight. Although the relative height the two groups were similar, data are not yet available their relative weights at the time one group shifted to requiring less physical activity.

In the 16-year follow-up period afforded to study, death fr from coronary heart disease were 55 per 10,000 person ye experience for longshoremen who were physically active lean, 59 for those less active and lean, 64 for the active fat, and 99 for the less active and fat. This represents a p tentiating effect on coronary mortality from job-related phy ical inactivity and heavier weight for height.

Questions similar to Dr. Chretien's can be asked for oth high-risk factors. For example, do longshoremen with high blood-pressure levels seek out physically less active jobs b cigarette smokers? Such questions invited the analyses sho in Figure 6 of our paper (N.E.J.M. 282:1109-1114, 19 which surveyed coronary death rates for all paired combi tions of four high-risk factors. It showed more than an ov lapping influence, indicating at least partial independence the factors on coronary mortality. Each of the six possi pairings of high-risk factors increased longshoremen's risk coronary death by more than additive amounts over the ri in the absence of the pair.

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TABLE 3.—*Sudden death from coronary heart disease related to smoking*

(Mortality ratios—actual number of deaths shown in parentheses)

Author, year, country, reference	Number and type of population	Data collection	Follow-up years	Number of deaths	Cigarettes/day	Cigars, pipes	Comment
Pooling Project, American Heart Association, 1970, U.S.A. (61).	7,427 white males 30-39 years of age at entry.	Medical examination and follow-up.	10	145	Never smoked .....1.00 (16) ≤10 .....1.98 (23) 20 .....1.98 (60) >20 .....3.86 (44)	1.00 (15) 1.26 (13)	See table 1 for description of Pooling Project.

TABLE 4.—*Coronary heart disease morbidity as related to smoking*

(Risk ratios—actual number of CHD manifestations shown in parentheses)[1]

[SM = Smokers NS = Nonsmokers EX = Ex-smokers]

PROSPECTIVE STUDIES

Author, year, country, reference	Number and type of population	Data collection	Follow-up years	Number of incidents	Cigarettes/day
Doyle et al., 1964, U.S.A. (61).	2,282 males Framingham, 30-62 years of age. 1,913 males Albany, 30-65 years of age.	Detailed medical examination and follow-up.	10	243 myocardial infarctions and CHD deaths.	NS .....1.00 (62) All smokers ....2.36 (191) <20 .....1.98 (44) 20 .....2.85 (64) >20 .....3.04 (83)
Gasmier et al., 1966, U.S.A. (277).	1,329 CHD-free male employees of Peoples Gas Company 40-59 years of age.	Interview and examination with clinic follow-up.	4	46 CHD	NS .....1.00 (2) <10 cigarettes, < 5 cigars, < 5 pipes ....2.92 (6) 10-19 cigarettes ....3.67 (8) >20 cigarettes, > 5 cigars, > 5 pipes 3.83 (29)
Epstein, 1967, U.S.A. (61).	6,165 male and female residents of Tecumseh, Mich.	Initial medical examination and repeat follow-up examinations.	4	96 male, 92 female CHD including deaths, angina, and myocardial infarctions.	*Males* *40-59* NS .....1.00 (1) EX .....4.53 (10) Cigarettes .....5.20 (36) *Females* NS .....1.00 (21) EX .....0.89 (3) Cigarettes 1.02 (14)

PROSPECTIVE STUDIES—Continued

Pipes, cigars	Age variation	Comments
		Data include CHD deaths, only on males 40-49 years of age and free of CHD on entry. NS includes pipes, cigars, and ex-smokers.
		NS includes ex-smokers. Includes all CHD.
Males—Continued *60 and over* 1.00 (7) 1.27 (11) 1.96 (23) *Females*—Continued 1.00 (47) 1.81 (8) 0.42 (2)	*Males* *40-59* SM ....1.00 (2) *60 and over* SM 0.86 (6)	Reexamination of patients was spread over 1½-6-year period, but data are reported in terms of 4-year incidence rates. Actual number of CHD incidents derived from data on incidence and total in smoking class.

[1] Unless otherwise specified, disparities between the total number of manifestations and the sum of the individual smoking categories are due to the exclusion of either occasional, miscellaneous, mixed, or ex-smokers.

(61) EPSTEIN, F. H. Some uses of prospective observations in the Tecumseh Community Health Study. Proceedings of the Royal Society of Medicine 60(1): 4-8, January 1967.

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TABLE 4.—*Coronary heart disease morbidity as related to smoking (cont.)*

(Risk ratios—actual number of CHD manifestations shown in parentheses)[1]
[SM = Smokers NS = Nonsmokers EX = Ex-smokers]

PROSPECTIVE STUDIES

Author, year, country, reference	Number and type of population	Data collection	Follow-up years	Number of incidents	Cigarettes/day
...enkins, et al., 1966, U.S.A. (90).	3,152 males 30-59 years of age at entry.	Initial medical examination and follow-up by repeat examinations.	4½	104 myocardial infarctions.	NS .....1.00 (21) EX .....2.47 (15) Current .....2.78 (63) 0-15/day .....†1.33 (43) >16 .....3.06 (59)
...annel, et al., 1968, U.S.A. (84).	8,127 males and females 30-59 years of age.	Medical examination and follow-up.	12	226 myocardial infarctions. 880 CHD.	*Myocardial infarction* *Males* NS .....1.00 (21) All SM .....1.51 (153) Heavy SM .....1.85 (53) *Risk of CHD (overall)* *Males* NS .....1.00 (61) 5-16 .....1.24 (25) 13-20 .....1.29 (90) >20 .....2.41 (76)
...onapiro et al., 1969, U.S.A. (378).	110,000 male and female enrollees of Health Insurance Plan of Greater New York (HIP) 35-64 years of age.	Baseline medical interview and examination and regular follow-up.	5	Total unspecified.	*Males* NS .....1.00 All current cigarettes .....2.14 (p<0.01) <20 .....1.50 >20 .....2.33 >40 .....6.26
...eys 1970 Yugoslavia Finland Italy Netherlands Greece (211).	9,184 males in 5 countries 40-59 years of age at entry.	Interviews and regular follow-up examination by local physicians.	5	65 deaths. 80 myocardial infarctions. 128 angina pectoris. 155 other †428 total.	NS, EX (SM <20) ...1.60 (305) All current (>20) 1.33 (103)

PROSPECTIVE STUDIES—Continued

Pipes, cigars	Age variation			Comments
(p<0.001)		30-49	50-59	†Includes nonsmokers and ex-smokers. NS includes former pipe and cigar smokers.
	NS.....1.00 (4)		1.00 (4)	
(p<0.001) (comparing 0-15 and 16+)	Current 4.23 (35)		2.26 (33)	

Myocardial infarction—Continued

Females
1.00 (11)
1.71 (23)

Risk of CHD (overall)—Continued

Females
1.00 (89)
0.86 (18)
1.29 (18)
0.88 (3)

Females	*Males only*	*Males* 35-44	45-54	55-64	*Females* 35-44	45-54	55-64	Total myocardial infarction includes those dead within 48 hours.
1.00	NS 1.00	1.00	1.00	1.00	1.00	1.00	1.00	
2.00	SM 1.52	2.47	3.06	1.69	2.25	2.37	1.80	
(p>0.01)	(p<0.01)	0.52	2.15	1.32	1.25	2.31	1.65	
1.27		3.04	3.29	1.81				
6.92		10.00	7.68	5.50	20.25	11.78	4.87	NS include ex-smokers.

Includes all CHD incidence including EKG diagnoses. Covers all countries investigated except U.S.A.
† Difference between total CHD and the sum of smoke groups is due to difference in figures presented by authors.

[1] Unless otherwise specified, disparities between the total number of manifestations and the sum of the individual smoking categories are due to the inclusion of either occasional, miscellaneous, mixed, or ex-smokers.

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TABLE 4.—*Coronary heart disease morbidity as related to smoking (cont.)*

(Risk ratios—actual number of CHD manifestations shown in parentheses)[a]
[SM = Smokers NS = Nonsmokers EX = Ex-smokers]

PROSPECTIVE STUDIES						PROSPECTIVE STUDIES—Continued				
Author, year, country, reference	Number and type of population	Data collection	Follow-up years	Number of incidents	Cigarettes/day	Pipes, cigars	Age variation			Comments
Taylor, et al. 1970 U.S.A. (*[illegible]*).	2,671 male railroad employees 40–59 years of age at entry.	Interviews and regular follow-up examination.	5	46 deaths. 83 myocardial infarctions. 78 angina pectoris. 86 other CHD. 212 total.	NS and EX ....1.00 (62) All current 1.77 (150)					All CHD including EKG diagnoses.
Dayton et al., 1970, U.S.A. (*48, 49*).	422 male U.S. veterans participating as controls in a clinical trial of a diet high in unsaturated fat.	Interviews and routine follow-up examinations.	up to 8	22 sudden deaths. 44 definite myocardial infarctions.	<10 .....1.00 (25) 10–20 .....1.04 (22) >20 .....1.17 (13)					No data on NS as a separate group.
Dunn et al., 1970 U.S.A. (*55*).	13,145 male patients in periodic health examination clinics.	Data only on new incidents extracted from clinic records.	up to 16	Total unspecified.			*30–39*	*40–49*	*50–59*	† Includes NS, EX, and <20 cigarettes/day. ‡ >20 cigarettes/day. Includes all CHD but excludes death. No data available comparing smokers and nonsmokers.
							†Low SM	1.00(25)	1.00(125)	1.00(157)
							‡High SM	2.17(10)	0.90 (31)	1.41 (53)
Pooling Project, American Heart Association 1970, U.S.A. (*[illegible]*).	7,427 white males 30–59 years of age at entry.	Medical examination and follow-up.	10	538 Includes fatal and nonfatal myocardial infarction and sudden death.	Never smoked ..1.00 (63) <10 .....1.65 (72) 20 .....2.08 (205) >20 .....2.28 (154)		1.00(63) 1.25(64)			
Paul et al., 1963, U.S.A. (*[illegible]*).	1,959 Western Electric Co. male workers participating in a prospective study for 4½ years.	Screening examination and history.			*Coronary cases (47)* NS ..... 23 1–7 ..... 2 8–12 ..... 9 13–17 ..... 6 18–22 ..... 47 23–27 ..... 3 >28 9	*Noncoronary controls (1,744)* 33 7 11 12 20 2 6 (p<0.005)				88 developed clinical coronary disease, 47 angina pectoris, 28 myocardial infarction, 13 deaths CHD

[a] Unless otherwise specified, disparities between the total number of manifestations and the sum of the individual smoking categories are due to the exclusion of either occasional, miscellaneous, mixed, or ex-smokers.

(*48*) DAYTON, S., PEARCE, M. L. Diet and atherosclerosis. Lancet 1(7644): 473–474, February 23, 1970.

(*49*) DAYTON, S., PEARCE, M. L., HASHIMOTO, S., DIXON, W. J., TOMIYASU, U. A Controlled Clinical Trial of a Diet High in Unsaturated Fat in Preventing Complications of Atherosclerosis. Circulation 40(1 Supplement 11), July 1969. 63 pp.

(*55*) DUNN, J. P., IPSEN, J., ELSOM, K. O., OHTANI, M. Risk factors in coronary artery disease, hypertension and diabetes. American Journal of the Medical Sciences 259(5): 309–322, May 1970.

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Diet and Atherosclerosis. The article of (48) Dayton and Pearce has provoked some comments from the authors (Lancet 28 February 1970).

DIET AND ATHEROSCLEROSIS

SIR,—The leading article (Nov. 1, p. 919) in which you discussed our trial[1] of a diet high in unsaturated fat made it clear that our report had not dealt adequately with at least one crucial question. Specifically, your article suggested that the low incidence of atherosclerotic events in participants on the experimental diet might have been due to the chance inclusion of a smaller number of heavy cigarette smokers in that group than in the control group. In order to satisfy ourselves and others on this point, we have undertaken further analysis of our results in relation to smoking habits. The results of this analysis, reported below, provide convincing evidence that differences in smoking habits could not have accounted for the favourable experience of subjects on the experimental diet.

We have examined the question by stratifying the subjects on the basis of cigarette-smoking habits as reported at the time of entry into the trial. The outcome experience of the control and experimental groups was then compared within each stratum. Incidence of the primary end-point (ischæmic heart-disease manifested by sudden death or by definite myocardial infarction) was expressed in terms of

1. Dayton, S., Pearce, M. L., Hashimoto, S., Dixon, W. J., Tomiyasu, U. American Heart Association Monograph no. 25. New York, 1969.

TABLE I—NUMBERS AND INCIDENCE-RATES OF MAJOR END-POINTS, STRATIFIED BY CIGARETTE-SMOKING HABITS AT ENTRY INTO THE TRIAL

Cigarette use at entry into study	Control group		Experimental group	
	No. of subjects	Incidence* per 100 man-years	No. of subjects	Incidence* per 100 man-years
Less than 10 cigarettes per day:				
No. of men in subgroup..	166	..	164	..
S.D. or M.I.	25	2·45	21	2·02
S.D., M.I., or C.I.	32	3·13	25	2·40
Any "hard" end-point†	32	3·13	27	2·60
Fatal atherosclerotic events	20	1·95	18	1·73
10–20 cigarettes per day:				
No. of men in subgroup..	129	..	173	..
S.D. or M.I.	22	2·56	20	1·76
S.D., M.I., or C.I.	30	3·49	21	1·85
Any "hard" end-point ..	34	3·95	25	2·20
Fatal atherosclerotic events	26	3·02	19	1·67
More than 20 cigarettes per day:				
No. of men in subgroup..	70	..	45	..
S.D. or M.I.	13	2·66	8	1·70
S.D., M.I., or C.I.	17	3·73	9	2·04
Any "hard" end-point ..	20	4·39	9	2·04
Fatal atherosclerotic events	16	3·51	9	2·04
Not known:				
No. of men in subgroup	57	..	42	..
S.D. or M.I.	5	1·24	6	1·95
S.D., M.I., or C.I.	8	1·99	8	2·60
Any "hard" end-point ..	10	2·48	8	2·60
Fatal atherosclerotic events	8	1·99	5	1·62
All subjects:				
No. of men in group ..	422	..	424	..
S.D. or M.I.	65	2·87	55	1·87
S.D., M.I., or C.I.	87	3·18	69	2·16
Any "hard" end-point..	96	3·51	66	2·38
Fatal atherosclerotic events	70	2·55	46	1·73

* A man with more than one event at the category cited was counted once only.

† Includes those events cited in the preceding footnote, plus the following: interruption of an extremity due to ischæmic gangrene, ruptured aneurysm, arterial infection.

S.D. = sudden death due to ischæmic heart-disease.
M.I. = definite myocardial infarction (overt or silent).
C.I. = definite cerebral infarction.

TABLE II—ESTIMATED "SMOKING-ADJUSTED" INCIDENCE OF MAJOR END-POINTS FOR TOTAL STUDY POPULATION

Clinical incident	Adjusted number of subjects affected		Adjusted incidence per 100 man-years	
	Control	Exper.	Control	Exper.
S.D. or M.I.	65·5	52·1	2·38	1·88
S.D., M.I., or C.I. ..	87·8	60·6	3·20	2·18
Any "hard" end-point ..	96·7	66·1	3·52	2·38
Fatal atherosclerotic events ..	70·8	48·3	2·58	1·74

subjects affected per 100 man-years. Incidence rates were also calculated for major end-points in combination.

As indicated in table I, at any of the three levels of cigarette consumption examined, the incidence of clinical events attributable to atherosclerosis was lower in experimental subjects than in individuals on the control diet. Thus when cigarette consumption is the same, the effect of the experimental diet persists.

Although table I makes it clear that there was a dietary effect, whatever the inequalities of the smoking distribution, it is also desirable to determine whether the surplus of heavy smokers in the control group accounted, *in part*, for the more favourable experience of the experimental group. Toward this end, we have developed estimates of "smoking-adjusted" incidence rates—that is, estimates of the outcome which would have resulted if the subjects of each smoking stratum had been allocated in equal numbers to the control and experimental groups. This was done by multiplying the number of subjects affected in a given cigarette-smoking stratum of the control group by $(x+c)/2c$, in which c = number of control subjects in the stratum and x = number of experimental subjects in the stratum; and by making a corresponding calculation for the experimental group. Resulting figures for all strata were totalled. Figures for total man-years at risk were similarly adjusted before calculating the adjusted incidence-rates. The objective of the calculation is to estimate the answer to this question: if a given stratum of a control group contains $1/2\,(c+x)$ subjects, whose mean experience is similar to that of the c subjects actually allocated to that subgroup; and if a corresponding experimental subgroup likewise contains $1/2\,(c+x)$ subjects, with mean experience comparable to that of the x subjects actually observed; and if this is true for all smoking strata, then what is the predicted outcome of such a trial? The resulting estimates, given in table II, are nearly identical to the figures actually observed (bottom of table I), the surplus of heavy smokers in the control group having been fully offset by an even larger surplus of moderate smokers (10–20 cigarettes per day) in the experimental group. We conclude, therefore, that the uneven distribution of cigarette-smoking habits had no net effect whatsoever on the outcome of the trial.

Returning to table I, the outcome in the control group reveals the well-known correlation between cigarette smoking and incidence of atherosclerotic complications. The smoking effect is not apparent, however, in the group on experimental diet; indeed, the experience of heavy-smoking experimental subjects was no worse than that of light-smoking and non-smoking subjects on either diet. Whether this is a true interaction between a dietary effect and smoking habits is difficult to judge with confidence on the basis of these observations. A true interaction of this nature, if confirmed by future work, would have important practical and theoretical implications. However, Leren's secondary-prevention trial[2] did not show evidence of interaction between the smoking effect and the diet effect. The reports of other dietary trials have not, to our knowledge, dealt with this question.

2. Leren, P. *Acta med. scand.* 1966, suppl. no. 466.

In referring to a "rebound" in serum-cholesterol levels on resumption of normal diet by experimental subjects, your article conveys a disturbing misinterpretation of our observations. As indicated in fig. 20 of our report, we tested this question by selecting the 10 experimental subjects and the 11 control subjects who had had the best and most prolonged adherence. During the 8 months before termination of the experimental diet, these two subgroups had nearly identical mean serum-cholesterol concentrations. This must be attributed to chance, since the larger groups from which the sub-samples were drawn displayed lower mean levels among the experimental subjects than among the controls (see fig. 5 of our report). On resumption of the regular diet, the experimental subgroup displayed a prompt serum-cholesterol rise comparable in magnitude to the fall seen at the start of the study. Their levels were now higher than those of the control subgroup. This was surely not a "rebound" phenomenon, but rather an expression of the fact that non-dietary influences had set serum-cholesterol levels higher in these 10 experimental subjects than in the 11 men with whom they were compared.

Wadsworth Veterans Administration Hospital and U.C.L.A. School of Medicine, Los Angeles, California.

SEYMOUR DAYTON
MORTON LEE PEARCE.

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TABLE 5.—*Coronary heart disease morbidity as related to smoking—angina pectoris—prospective studies*

(Risk ratios—actual number of CHD manifestations shown in parentheses)[1]

(SM = Smokers NS = Nonsmokers)

Author, year, country, reference	Number and type of population	Data collection	Follow-up years	Number of incidents	Cigarettes/day	Cigars and pipes	Age variation	Comments
Doyle et al., 1964, U.S.A. (56).	2,282 males, Framingham, 30-62 years of age. 1,913 males, Albany, 39-55 years of age.	Detailed medical examination and follow-up.	10 8	81	NS .....1.00(30) All .....1.09(51) <20 .....1.17(15) 20 .....0.59(18) >20 .....1.18(18)			NS include ex-smokers and pipe and cigar smokers.
Jenkins et al., 1968, U.S.A. (60).	3,182 males aged 39-59 at entry.	Initial medical examination and follow-up by repeat examination.	4½	28	NS .....1.00 (8) All current cigarettes .....1.44(16) >16 .....1.63(14)			NS include former pipe and cigar smokers.
Kannel et al., U.S.A. (94).	5,127 males and females years of age 30-59	Medical examination and follow-up.	12	107	*Males* NS .....1.00(16) Heavy SM, >20 cigarettes .....2.04(17) *Females* NS .....1.00(55) Cigarette SM .....0.65(16)			
Shapiro et al., 1969, U.S.A. (272).	110,000 male and female enrollees of New York City HIP 35-64 years of age.	Baseline medical interview and examination and regular follow-up.	8	Total Unspecified	*Males* *Females* NS .....1.00 1.00 Current cigarettes †1.91 1.20 <40 .....1.51 } 1.20 >40 .....4.86 }	*Males* NS...1.00 SM...21.71	*Males* *35–44 45–54 55–64* NS .....1.00 1.00 1.00 Current cigarettes ..3.40 1.67 2.06 <40 .....2.35 1.40 1.54 >40 .....10.15 2.65 6.15 *Females* NS .....1.00 1.00 1.00 Current cigarettes ..1.56 1.67 0.97 <40 .....1.67 1.53 1.04 >40 ..... — 4.12 —	†(p<0.01) ‡(p<0.05) NS include ex-smokers.

[1] Unless otherwise specified, disparities between the total number of manifestations and the sum of the individual smoking categories are due to the exclusion of either occasional, miscellaneous, mixed, or ex-smokers.

Numerous epidemiological studies have indicated that cigarette smokers have increased mortality ratios for CHD; that is, cigarette smokers show significantly increased death rates compared with nonsmokers (table 2). The risk incurred by cigarette smoking increases with increasing dosage and, as measured by mortality ratios, is more marked for men in the younger age groups, under age 60, although the absolute increment in death rates experienced by smokers over that of nonsmokers continues to increase with increasing age. Table 2 lists the mortality ratios found in the major studies. Certain of these studies, including those at Framingham, Massachusetts, the Health Insurance Plan of New York City (HIP), and at Tecumseh, Michigan, have analyzed morbidity as well as mortality from CHD and have indicated that the risk of developing fatal and nonfatal CHD is greater among cigarette smokers than among nonsmokers (tables 3 and 4). Conflicting evidence has been published concerning the relationship of cigarette smoking and the incidence of angina pectoris. While some

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studies have shown an increased risk of this manifestation among smokers, others have not (see table 5).

From these longitudinal studies, it has become increasingly clear that cigarette smoking is one of several risk factors for CHD and that it exerts both an independent effect and an effect in conjunction with the other risk factors. The basic concept may be expressed as follows: The more risk factors a given individual has, the greater the chance of his developing CHD. The importance of the constellation of coronary risk factors which include cigarette smoking, high blood pressure, and high serum cholesterol in predicting the risk for CHD is illustrated in figures 1 through 3. Other risk factors are included in certain of these figures and are discussed below.

Knowledge of the effects of cigarette smoke on the cardiovascular system has developed concurrently with the knowledge derived from the epidemiological studies. Nicotine, as well as cigarette smoke, has been shown to increase heart rate, stroke volume, and blood pressure, all most probably secondary to the promotion of catecholamine release from the adrenal gland and other chromaffin tissue. This release of catecholamines is also considered to be the cause of the rise in serum free fatty acids observed upon the inhalation of cigarette smoke. Studies concerning the effect of nicotine on cardiac rhythm have also suggested that smoking might contribute to sudden death from ventricular fibrillation.

In addition, research efforts have also been directed toward the effects of smoking on blood clotting and thrombosis; since many cases of sudden death and myocardial infarction are associated with thrombosis in a diseased coronary artery branch. Cigarette smoking may be associated with increased platelet aggregation *in vitro* and thus might play a role in the development of such thrombi or platelet plugs *in vivo*.

Other mechanisms have been investigated. Because cigarette smoking has been shown in some studies to be related to the prevalence of angina pectoris as well as to the incidence of myocardial infarction, it has been suggested that smoking enhances the development of atherosclerotic lesions. Autopsy and experimental studies have shown that cigarette smoking plays a role in atherogenesis. The administration of nicotine has been observed to increase the severity of cholesterol-induced atherosclerotic lesions in experimental animals. Attention is presently being given to carbon monoxide, which is present in cigarette smoke in such concentrations as to cause carboxyhemoglobin concentrations in the blood of smokers as high as 10 percent. Based on research in animals, it is reasonable to conclude that the atherosclerotic process may be enhanced, in part, by the relative arterial hypoxemia in cigarette smokers caused by the increased carboxyhemoglobin level.

With respect to the acute event of myocardial infarction, attention has been focused on the role of nicotine. Nicotine stimulates the myocardium, increasing its oxygen demand. Other experiments have demonstrated that in the face of diminished coronary flow (due to partial occlusion from severe atherosclerosis in man or to partial mechanical obstruction in the animal), nicotine does not lead to an increase in coronary blood flow as seen in the normal individual. These effects exaggerate the oxygen deficit when the supply of oxygen has already been decreased by the presence of carboxyhemoglobin. Thus, a marked imbalance between oxygen demand (which has been increased) and oxygen supply (which has been decreased) is created by the inhalation of CO and nicotine. This imbalance may contribute to acute coronary insufficiency and myocardial infarction.

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EPIDEMIOLOGICAL STUDIES

Numerous epidemiological studies, both retrospective and prospective, have been carried out in various countries in order to identify the risk factors associated with the development of coronary heart disease (CHD). Many of these studies have included smoking as one of the variables investigated. Tables 2 to 4 present the major findings.

CORONARY HEART DISEASE MORTALITY

Table 2 lists the various prospective studies concerning the relation of CHD mortality and smoking. These studies demonstrate the dose-related effect of cigarette smoking on the risk of developing CHD. For example, the Dorn Study of U.S. Veterans as reported by Kahn (*93*) reveals progressively increasing mortality ratios, from 1.39 for those smoking 1 to 9 cigarettes per day to 2.00 for those smoking more than 39 cigarettes per day. Although the data are not detailed in the accompanying tables, several of these studies have also shown that increased rates of CHD mortality are associated with increased cigarette dosage, as measured by the degree of inhalation and the age at which smoking began. Although not as striking, the data for females reveal the same trends.

In most studies, the smokers' increased risk of dying from CHD appears to be limited mainly to those who smoke cigarettes. Some studies that have investigated other forms of smoking have shown much smaller increases in risk for pipe and cigar smokers when compared to nonsmokers. However, the recent study by Shapiro, et al. (*172*) of a large population enrolled in the Health Insurance Plan (HIP) of New York City showed a significantly increased risk for the development of myocardial infarction and rapidly fatal myocardial infarction for a group consisting of both pipe and cigar smokers.

Table 3 details the findings of the American Heart Association Pooling Project on sudden death. The Pooling Project, a national cooperative project of the AHA Council on Epidemiology, is described in table 1 (*88*). Cigarette smokers in the 30 to 59 year age group incurred a risk of sudden death from CHD substantially greater than that of nonsmokers. Pipe and cigar smokers were observed to show a risk slightly greater than that of nonsmokers (table 3).

The relative risk of CHD mortality is greatest among cigarette smokers (as well as among those with other risk factors) in the younger age groups and decreases among the elderly. In table 2, Hammond and Horn found that for those smoking more than one pack per day, the risk is 2.51 in the 50 to 54 year age group and 1.56 in the 65 to 69 year age group. Although the relative risk for CHD among smokers decreases in the older age groups, the actual number of excess deaths among smokers continues to climb since the differences in death rates between smokers and nonsmokers continue to rise.

(*93*) KAHN, H. A. The Dorn study of smoking and mortality among U.S. veterans: report on 8½ years of observation. IN: Haenszel, W. (Editor). Epidemiological Approaches to the Study of Cancer and Other Chronic Diseases. Bethesda, U.S. Public Health Service, National Cancer Institute Monograph No. 19, January 1966, pp. 1-125.

TABLE 19.—*Autopsy studies of atherosclerosis (cont.)*

[Figures in parentheses are number of individuals in that smoking category][1]

[SM = smokers NS = nonsmokers]

Author, year, country, reference	Autopsy population	Data collection	Cigarettes per day	Conclusions	Comments
[illegible] et al., 1962 Chile (*[illegible]*).	1,160 males and 290 females who died violently in 1961-1964. Smoking information available only on 566 males.	Interview with relatives.	The results concerning internal fibrous streaks and fatty plaques in the left anterior descending coronary artery are reported in graphic form only. An examination of this data indicates that the moderate and heavy smokers appeared to show consistently higher percentages of diseased areas than the nonsmokers. But the statement of the authors implies that these differences were not statistically significant when subjected to an analysis of variance.	The authors conclude that: "No relationship between atherosclerotic lesions and the use of tobacco was discernible."	
[illegible] et al., 1969 U.S.A. (*[illegible]*).	747 males 20-64 years of age autopsied between 1963-1968 at Charity Hospital in New Orleans.	Interview with next of kin within 8 weeks of death.	*Basal Group (excluding diseases related to smoking or CHD). Mean percentage of coronary artery internal surface involved with raised lesions (number of cases).*	The authors conclude that: "Atherosclerotic involvement of aorta and coronary arteries is greatest in heavy smokers and least in nonsmokers."	This report concerns only ages 25-64. No data on statistical significance provided.

	25-34	35-44	45-55	55-64
White				
NS	3 (5)	10 (14)	20 (6)	30 (11)
1-24 cigarettes/day	9 (14)	17 (10)	26 (16)	33 (7)
>25 cigarettes/day	12 (8)	31 (14)	26 (25)	33 (20)
Negro				
NS	4 (11)	8 (8)	16 (11)	17 (18)
1-24 cigarettes/day	3 (23)	11 (31)	14 (30)	26 (22)
>25 cigarettes/day	17 (10)	14 (17)	29 (12)	16 (11)

[1] Unless otherwise specified, disparities between the total number of individuals and the sum of the individual smoking categories are due to the exclusion of either occasional, miscellaneous, mixed, or ex-smokers.

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Epidemiological Studies Criticized by Seltzer. The appraisal of the Royal College of Physician's Report by Seltzer (Lancet 1: 243-248, 1972) applies to the 1971 document. This was in turn followed by:

1. A letter from Fletcher (Lancet 12 February, 1972).
2. A letter from Sterling (Lancet 29 April, 1972).
3. A letter from Seltzer (Lancet 11 March, 1972).
4. A letter from Burch (Lancet 10 June, 1972).
5. A letter from Fletcher (Lancet 1 July, 1972), and finally
6. A letter from Doll (Lancet 15 July, 1972).

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Occasional Survey

CRITICAL APPRAISAL OF THE ROYAL COLLEGE OF PHYSICIANS' REPORT ON SMOKING AND HEALTH

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Summary The claims in the Royal College of Physicians' report *Smoking and Health Now* are examined with reference to certain secular changes in mortality for British doctors as compared with those for the general population. The data as presented are found to exhibit geographical and populational restrictions, age restrictions, and unexpected changes in classification of diseases; they also omit a crucial time period and assume certain unverified trends in smoking habits. The statements and claims of the Royal College of Physicians are not supported by the re-examination of certain data included in the report, and by an analysis of pertinent data that were omitted. The appraisal of the full data illustrates the hazards of drawing firm conclusions from secular changes in death-rates, and raises doubts that the Royal College of Physicians' report contains the "strongest evidence there is of the value of giving up cigarettes".

INTRODUCTION

IN 1971 the Royal College of Physicians (R.C.P.) issued a report entitled *Smoking and Health Now*.[1] A table in that report contained secular comparisons for the death-rates during 1953–57 and 1962–65 of two groups of men at ages 35–64. One group was taken from R. Doll and A. B. Hill's sample of British doctors; the other group was assembled from the Registrar General's data for England and Wales. According to the R.C.P. report, the contrasted data constitute "the strongest evidence there is of the value of giving up cigarettes".

The interpretation of secular changes in mortality is a difficult statistical procedure. As Bradford Hill has stated, "In making comparisons between death-rates from different causes at different times . . . it must be realised that one is dealing with material which is, in Raymond Pearl's words, 'fundamentally of a dubious character'".[2] Secular changes in these rates may be affected by vagaries of death-certificate reporting, such as accuracy of diagnosis, faulty certifications of death, and trends in reporting; and also by influences related to sex, race, socioeconomic status, geography, and occupation. The uncertain effects of these features are difficult to exclude when a specific exogenous factor is held responsible for the observed secular changes.

Because the comparison of secular death-rates is often an important technique in epidemiological analysis, and because the results of such a comparison have been made a central issue in the R.C.P. report, the validity of the statistical procedures has been appraised here.

CLAIMS OF THE R.C.P.

The R.C.P. drew its conclusions mainly from data in table 2.3 of its report (reproduced here in table 1), and stated that:

(1) The death-rate of British doctors declined more than that of the general population in the interval between the time periods 1953–57 and 1962–65.

(2) In the category "major diseases related to cigarette smoking", the death-rates declined in British doctors but increased in the general population.

(3) In the category "all unrelated causes", the death-rates declined equally in British doctors and in the general population.

From data elsewhere in the report, the R.C.P. also stated that British doctors' cigarette smoking declined by about 50% between 1951 and 1965, but "there was little corresponding change in the smoking habits of the general population during the same period".

The associated secular changes in death-rates and

TABLE I—CHANGES IN DEATH-RATES PER 100,000, STANDARDISED FOR AGE IN DOCTORS AND IN ALL MEN AGED 35–64 IN ENGLAND AND WALES 1953–1957 AND 1962–1965 (REPRODUCED FROM R.C.P. TABLE 2.3)

Cause of death	Male doctors			All men in England and Wales		
	Period		% Change	Period		% Change
	1953–57	1962–65		1953–57	1962–65	
Coronary heart-disease	294	277	−6	219	290	+32
Other cardiovascular diseases	167	157	−6	185	152	−18
All cardiovascular diseases	461	434	−6	404	442	+ 9
Cancer of the lung	60	37	−38	113	120	+ 6
Chronic bronchitis	18	14	−22	74	71	− 4
Major diseases related to cigarette smoking	539	485	−10	591	633	+ 7
Other cancers*	130	99	−24	152	145	− 5
Other causes*	184	163	−11	250	188	−25
All unrelated causes	314	262	−17	402	332	−17
All causes	853	747	−12	993	966	− 3

* These include a small number of deaths from cancers of mouth, throat, and œsophagus, from tuberculosis, from cirrhosis of the liver, and from peptic ulcer, which are related to cigarette smoking but make only a small contribution to the excess deaths of cigarette smokers.

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in smoking were interpreted by the R.C.P. as follows. As cigarette smoking declined more for British doctors than for the general population, the death-rate between the two time-periods declined more for the doctors than for the general population. Furthermore, although the British doctors and the general population had similar changes in death-rates for diseases "unrelated" to cigarette smoking, the death-rates for the "major diseases related to cigarette smoking" declined for the doctors but rose for the general population. From these associations the R.C.P. concluded that "the benefit that British doctors have won at the peak of their professional careers provides the strongest evidence there is of the value of giving up cigarettes".

UNCERTAINTIES IN R.C.P. DATA

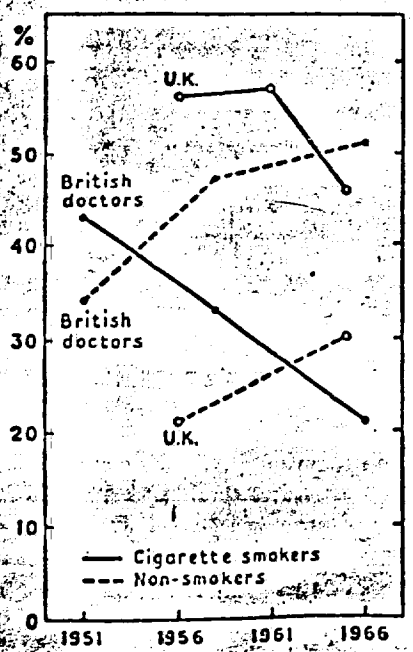
An examination of table I and the R.C.P. statements reveals several uncertainties and inconsistencies.

Data about Cigarette Smoking

According to the R.C.P. report, cigarette smoking between 1951 and 1965 declined among British doctors by about half (from 43% to 21%), and the proportion of non-smokers (including ex-smokers) rose from 34% to 51%. During this period, there was "a striking contrast between the smoking habits of doctors and those of other men [in the general population] over the age of 35 . . . [since] there was little corresponding change in the smoking habits of the general population during the same period".

The R.C.P. states that it obtained its data about the smoking habits of British doctors from the Doll and Hill 1964 study [3] and from Doll and M. C. Pike by personal communication. The R.C.P. source of its comments on the smoking habits of the men from the general population is clear for 1965 but not for the immediately prior periods. The figures for the smoking habits of United Kingdom men in 1965 were those published by the Tobacco Research Council (T.R.C.).[4]

The figure indicates the changes in the smoking habits of British doctors and United Kingdom men of the same ages between 1951 and 1966. For the sake of clarity, forms of smoking other than non-smoking and cigarette smoking have been omitted. (Following the procedures of the R.C.P., non-smokers consist of never-smokers and ex-smokers, while cigarette smokers refer to cigarette smokers only.) The data with regard to British doctors are those presented by the R.C.P. (in its fig. 1.4); the U.K. data for 1965 are those derived by the R.C.P. from T.R.C. data [4]; U.K. figures for 1961 have been derived by me from the same source,[4] and those for 1956 have been obtained from an earlier research paper of the Tobacco Research Council.[5] Earlier U.K. data (in the same form) for 1951–55 are not available from the Tobacco Research Council survey.



Changes in smoking habits of British doctors and men in U.K. aged 35 and over.

According to T.R.C. data, between 1951 and 1956 cigarette consumption per adult male in the U.K. increased by only 4%. This figure refers to cigarette consumption, not proportion of cigarette smokers; nevertheless, it seems reasonable to conclude that the proportion of cigarette smokers among U.K. men did not change strikingly between 1951 and 1956. After 1956, however, the proportion of non-smokers in the U.K. over the age of 35 increased by 15% (see figure), and the corresponding rise for British doctors was 19%. Cigarette smokers constituted 56% of the U.K. men in 1956 and 57% in 1961, but only 46% in 1965, a change of 19%. From 1961 to 1965, cigarette smoking among British doctors dropped by 19%. These findings receive further confirmation from R.C.P. fig. 1.1, which shows a drop in cigarette consumption among men in the U.K. population since 1960.

These data thus support the R.C.P.'s contention that the proportion of cigarette-smoking British doctors fell between 1951 and 1965, but they do not support the statement about "little corresponding change" in the general population. From 1956 to 1965, the non-smokers in the general population increased at a rate similar to that shown by British doctors. From 1961 to 1965 the percentage of cigarette smokers decreased at about the same rate in both the general population and the doctors.

Changes in Classification of Disease

Another interesting feature of the R.C.P. table is the classification of disease, which was done by the R.C.P. in a manner different from that of Doll and Hill. In Doll and Hill's published studies of British doctors in 1964 and 1966,[3,6] the diseases regarded as "related" to cigarette smoking were cancer of the lung and upper respiratory and digestive tracts, chronic bronchitis, coronary heart-disease, peptic ulcer, cirrhosis of the liver, and pulmonary tuberculosis. Under "unrelated causes", Doll and Hill included other cancers, other respiratory disease, cerebrovascular disease, other cardiovascular disease, violence, and other causes.

In the R.C.P. tabulation, many of Doll and Hill's "unrelated diseases" were transferred to the category of "related" diseases; thus among "major diseases related to cigarette smoking" are rheumatic fever, rheumatic pericarditis, endocarditis, and myocarditis, diseases of the mitral, aortic, and tricuspid valves, acute and subacute bacterial endocarditis, gangrene, varicose veins, and hæmorrhoids. These and other diseases listed by the R.C.P. under "other cardiovascular diseases" comprise numbers 400–468 (all diseases of the circulatory system, less 420) and 330–334 (vascular lesions affecting the central nervous system) of the International Statistical Classification of Diseases, Injuries and Causes of Death.[7]

No explanation is provided for these changes in the Doll/Hill classification, although the R.C.P. report relied so heavily on other aspects of the Doll/Hill data. Explanations were, however, provided for certain changes from "related" diseases to "unrelated" diseases.

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Geographic Restrictions

The R.C.P. compared death-rates for British doctors and for all men in England and Wales. The Doll/Hill sample of British doctors,[3] however, was drawn from the U.K. (Scotland and Northern Ireland, as well as England and Wales). The contrasted populations are thus geographically different: a more suitable comparison for the British doctors would be with all men in the United Kingdom, since the male death-rates of the U.K. may differ from those of only England and Wales.

Population Restrictions

Doctors are not typical of all men in England and Wales. They differ in race, social and economic status, "life style", education, and other characteristics that are themselves related to rates of disease and mortality, and that may affect trends in death-rates for the contrasted populations.

Age Restrictions

The R.C.P. data are restricted to men ages 35 to 64, although the data for all adult ages would ordinarily extend from ages 35 to 84. Since the R.C.P. statements are not confined to conclusions about the health of cigarette smokers only at ages 35–64, the absence of data for all adult ages would be a significant limitation on the R.C.P. conclusions.

Intermediate Time Period

The R.C.P. compared death-rates for the periods 1953–57 and 1962–65, omitting 1958–61. When two separated periods in time are compared without regard to the intervening period, any conclusions about a trend are tenuous, because the intermediate data may alter any trend found between the two extremes of time.

AUGMENTATION OF R.C.P. DATA

Apart from the uncertainties in the sampling of doctors, the unexplained changes in classification of disease, and the inaccurate description of smoking habits for the general population, the R.C.P. report did not consider the omissions just cited in geography, age, and time periods. Since the missing data might help clarify some of the issues, a reanalysis of the R.C.P. contentions seemed desirable, with the data expanded to include geographic, age, and temporal information that had been omitted in the R.C.P. report. The additional details for these features of the general population of the U.K. were obtained from the Registrar General's reports.[8] The corresponding details about the British doctors were obtained from the latest Doll and Pike report.[9]

TABLE III—% CHANGES IN AGE-STANDARDISED DEATH-RATES PER 100,000 FOR BRITISH DOCTORS AND ALL MEN IN ENGLAND AND WALES AGED 35–64*

Cause of death	British doctors		All men in England and Wales	
	From 1953–57 to 1958–61	From 1958–61 to 1962–65	From 1953–57 to 1958–61	From 1958–61 to 1962–65
Coronary heart-disease	− 7	+ 1	+15	+15
Other cardiovascular diseases	+18	−20	−10	− 9
All cardiovascular diseases	+ 2	− 8	+ 4	+ 5
Cancer of the lung	− 7	−34	+ 5	+ 1
Chronic bronchitis	−33	+17	− 1	− 3
Major diseases related to cigarette smoking	0	−10	+ 3	+ 4
Other cancers	− 6	−20	− 2	− 3
Other causes	+ 5	−16	−16	−11
All unrelated causes	+ 1	−17	−10	− 8
All causes	0	−13	− 2	− 1

* % changes are used in this form to conform with R.C.P. practice.

Missing Time Period

For the same ages and geography used in the R.C.P. report, the data of the missing time interval are shown here in table II. This table indicates the annual age-standardised rates per 100,000 men aged 35–64, for British doctors and all men in England and Wales during the three successive periods 1953–57, 1958–61, and 1962–65. In table III the "absolute" values shown in table II are converted into percentage changes in death-rates during the three time periods. The figures in tables II and III show the following results that are pertinent to the R.C.P. statement.

The claim that total death-rates of doctors declined more than those of the general population.—As shown

TABLE II—AGE-STANDARDISED ANNUAL DEATH-RATES PER 100,000 MEN, AGES 35 TO 64*
(ADAPTED TO DISEASE CLASSIFICATIONS OF R.C.P. TABLE 2.3)

Cause of death	British doctors			All men in England and Wales		
	1953–57	1958–61	1962–65	1953–57	1958–61	1962–65
Coronary heart-disease	294	273	277	219	252	290
Other cardiovascular diseases	167	197	157	185	167	152
All cardiovascular diseases	461	470	434	404	419	442
Cancer of the lung	60	56	37	113	119	120
Chronic bronchitis	18	12	14	74	73	71
Major diseases related to cigarette smoking	539	538	485	591	611	633
Other cancers	130	123	99	152	149	145
Other causes	184	193	163	250	211	188
All unrelated causes	314	316	262	402	360	332
All causes	853	854	747	993	971	966

* The data for the first and last time periods are taken from the R.C.P. report. The data for the middle time periods were derived from the Doll and Pike report.[9] For British doctors, the years run from Nov. 1 to Oct. 31. To maintain consistency with R.C.P. table 2.3, we have followed the R.C.P. labelling of the period years.

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Source: https://www.industrydocuments.ucsf.edu/docs/rrlk0000

in table III, the reduction in cigarette smoking among British doctors between 1953–57 and 1958–61 was not accompanied by any change in overall death-rate. During the same interval the death-rate for all men in England and Wales fell by 2%. Between 1958–61 and 1962–65, the total death-rates of British doctors fell more than those of the general population, although cigarette smoking from 1951 to 1965 declined at least as fast in terms of percentage among the general population than in British doctors. From 1958–61 to 1962–65, the reduction in total death-rates was 1% in the general population and 13% in the British doctors. Thus, when the three time periods are considered successively, the total death-rates of British doctors are not found to have declined consistently more than the general population.

The claim that death-rates for "all unrelated causes" declined equally in British doctors and in the general population.—This assertion is not supported by the data in tables II and III. From 1953–57 to 1958–61, the death-rates for "unrelated causes" among British doctors rose by 1% while those of the general population fell by 10%. From 1958–61 to 1962–65, the death-rates for these "unrelated causes" decreased by 17% in British doctors and by 8% in the general population.

The claim that death-rates for "major diseases related to cigarette smoking" declined in the British doctors but increased in the general population.—From 1953–57 to 1958–61, there was no drop in the death-rates of British doctors for "major diseases related to cigarette smoking". The rates were essentially the same: 539 and 538 per 100,000 men, respectively. For the same category of diseases over the same interval, the death-rates increased by 3% in all men in England and Wales. In the second interval, however, the R.C.P. claim is confirmed. The death-rates declined (−10%) in British doctors and rose (+4%) in the general population. The general population's increase in death-rates between 1958–61 and 1962–65 occurred, however, despite the concomitant reduction in cigarette smokers of this population between 1961 and 1965.

Inconsistencies in patterns of specific diseases.—Tables II and III contain several inconsistencies in the patterns of specific diseases—especially in the data of British doctors for changes in death-rates between the first interval (1953–57 to 1958–61) and the second interval (1958–61 to 1962–65). For example, in British doctors, the death-rate for coronary heart-disease declined in the first interval and rose in the second interval; the death-rates for "other cardiovascular diseases" and for "all cardiovascular diseases" rose substantially in the first interval and then fell substantially in the second. The rate for chronic bronchitis fell by 33% and then rose by 17%. For the categories of "all causes", "major diseases related to cigarette smoking", and "unrelated causes", the British doctors had almost no changes in the death-rates in the first interval, followed by notable decreases in the second interval. These inconsistencies occurred despite the almost constant rate of decline of cigarette smoking among British doctors from 1951 to 1966. For the general population of England and Wales, on the other hand, the trends of death-rates were strikingly consistent for the specific disease categories in both the first and second intervals despite the inconstant cigarette smoking patterns in this population. As previously noted, the proportion of cigarette smokers in the general population changed little between 1956 and 1961, but then dropped sharply from 1961 to 1965.

Missing geography.—The death-rates for all men in the United Kingdom ages 35–64 (in contrast to all men in England and Wales) have been derived for the missing period 1958–61 from the Registrar General's reports (table IV). These data permit a comparison of the death-rate changes for the two intervals (from 1953–57 to 1958–61 and from 1958–61 to 1962–65) in the men of the United Kingdom—a more suitable comparison for the sample of British doctors. In the data for U.K. men, the death-rates for all causes fell in the first interval (while smoking habits were essentially unchanged), and stayed virtually the same in the second interval (while smoking decreased). The death-rates for "related" diseases rose in the first period and continued to rise in the second. For "unrelated" diseases, the death-rate of U.K. men fell more in the first interval (−12%) than in the second (−8%). Thus, when the missing time period and missing geography are taken into consideration for ages 35–64, the claims of the R.C.P. are not substantiated. The discrepancies are most notable for the events of the first interval.

TABLE IV—AGE-STANDARDISED DEATH-RATES PER 100,000 IN BRITISH DOCTORS AND IN MEN OF UNITED KINGDOM

Deaths from	British doctors			United Kingdom		
	1953–57	1958–61	1962–65	1953–57	1958–61	1962–65
Ages 35–64:						
Related causes	539	538	455	586	614	639
Unrelated causes	314	316	262	425	375	346
All causes	853	854	747	1011	989	985
Ages 35–84:						
Related causes	1180	1231	1202	1401	1435	1473
Unrelated causes	560	570	528	817	762	719
All causes	1740	1801	1730	2218	2197	2192

Missing Ages

In this section, the data are expanded to include the missing ages (35–84) as well as the missing time period (1958–61).

Table V shows the death-rates of the British doctors and all men in England and Wales, ages 35–84, for the three successive time periods 1953–57, 1958–61, and 1962–65. The percentage changes over the two time intervals are presented in table VI. The figures in these tables show the following results that are pertinent to the R.C.P. statements.

Claim that total death-rates of doctors decline more than those of the general population.—In the age-groups 35–84, for the time periods considered by the R.C.P., the death-rates of British doctors did not consistently decline more than those of the general population. Between the two external time periods (1953–57 and 1962–65) the total death-rate of British doctors fell

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TABLE V—AGE-STANDARDISED ANNUAL DEATH-RATES PER 100,000 MEN, AGES 35–84*
(ADAPTED TO DISEASE CLASSIFICATIONS OF R.C.P. TABLE 2.3)

Cause of death	British doctors			All men in England and Wales		
	1953–57	1958–61	1962–65	1953–57	1958–61	1962–65
Coronary heart-disease	519	564	559	425	491	564
Other cardiovascular diseases	507	533	506	682	603	541
All cardiovascular diseases	1026	1097	1065	1107	1094	1105
Cancer of the lung	110	85	83	149	171	188
Chronic bronchitis	44	49	54	160	170	184
Major diseases related to cigarette smoking	1180	1231	1202	1416	1435	1477
Other cancers	253	236	224	307	301	294
Other causes	307	334	304	482	438	406
All unrelated causes	560	570	528	789	739	700
All causes	1740	1801	1730	2205	2174	2177

* British doctors' data derived from Doll and Pike.[4] For British doctors, the years run from Nov. 1 to Oct. 31. For reasons of consistency with R.C.P. table 2.3, we have followed the R.C.P. labelling of the period years.

by only 0·6% (1740 to 1730), as compared to a decline of 1·3% (2205 to 2177) in all men in England and Wales. When the additional age range and missing time periods are inspected, the death-rate for the British doctors is seen to have increased by 4% from 1953–57 to 1958–61, despite the concomitant decrease in cigarette smoking. Over the same interval the death-rates for the general population declined by 1%. From 1958–61 to 1962–65, British doctors' overall death-rate declined more than that of the general population, which showed essentially no change, despite the drop in cigarette smoking.

Claim that the death-rates for the category of "all unrelated causes" declined equally in British doctors and in the general population.—This claim is not supported by the data for ages 35–84. Between the external periods 1953–57 and 1962–65, the reduction in death-rates for "unrelated causes" in the general population (11%) was almost twice as great as the comparable decline in the British doctors (6%). When the data are examined for the effects of the missing time period, the R.C.P. contention is about right for the second time interval, but not for the first. In the first interval the death-rate for "unrelated causes" increased by 2% in the British doctors, in contrast to that of the general population, which showed a 6% drop.

Claim that the death-rates of "major diseases related to cigarette smoking" declined in British doctors but increased in the general population.—Again, this assertion is not fully supported by the data for ages 35–84. From the "outside" time periods, 1953–57 to 1962–65, the death-rates for "related" diseases increased in both populations, rising by 2% in British doctors and by 4% in all men in England and Wales. For the first "inside" interval, from 1953–57 to 1958–61, the data of ages 35–84 also do not support this R.C.P. contention. The death-rates for the classification "major diseases related to cigarette smoking" increased in both British doctors (4%) and in the general population (1%). In the second interval doctors' death-rates declined (2%) and the general population rates increased (3%). Thus, the apparent contradiction of a rising death-rate during a fall in smoking occurred in British doctors for the first interval and in the general population for the second.

TABLE VI—% CHANGES IN AGE-STANDARDISED DEATH-RATES PER 100,000 FOR BRITISH DOCTORS AND ALL MEN IN ENGLAND AND WALES AGED 35–84.

Cause of death	British doctors		All men in England and Wales	
	From 1953–57 to 1958–61	From 1958–61 to 1962–65	From 1953–57 to 1958–61	From 1958–61 to 1962–65
Major diseases related to cigarette smoking	+4	−2	+1	+3
All unrelated causes	+2	−7	−6	−6
All causes	+4	−2	−1	0

Inconsistencies in patterns of specific diseases.—An additional inconsistency in the R.C.P. data is noted for coronary heart-disease. For ages 35–84, the death-rates from 1953–57 to 1962–65 in British doctors increased by 8% during a period of declining cigarette smoking. In addition, although the category of "other cardiovascular diseases" showed no change in British doctors aged 35–84 between the same two periods, the death-rates for the same diseases declined by 21% in all men in the general population of England and Wales. The death-rates for "all cardiovascular disease" increased by 4% in British doctors aged 35–84, in contrast to essentially no change for all men in England and Wales. Other inconsistencies occur in the patterns of specific diseases in the expanded age-and-time data. In British doctors, the death-rates for coronary heart-disease, for "other cardiovascular diseases", and "all cardiovascular disease" increased in the first interval and decreased in the second. Despite a constant decline in doctors' cigarette smoking, cancer of the lung decreased by 23% over the first interval and by only 2% in the second interval.

With respect to all men in England and Wales, the trends in death-rates for the specific diseases are quite consistent in both the first and second intervals, despite the inconstant changes in smoking habits in the general population.

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Missing geography.—The bottom part of table IV summarises the expanded geographical data for the augmented age and time intervals. The lower half of this table shows the age-standardised death-rates per 100,000 men ages 35–84 for British doctors and for all men in the United Kingdom during the successive periods 1953–57, 1958–61, and 1962–65. The data show differences in the death-rates for the men in the United Kingdom as compared to corresponding results for the men in England and Wales shown in table V. The basic trend in the changes from one time period to the next for the United Kingdom men are not appreciably different from those found in the corresponding figures for England and Wales. Consequently, it seems reasonable to conclude that the omissions in age and time period, rather than geography, are responsible for any distortions or discrepancies in the claims of the R.C.P.

DISCUSSION

The statements and claims of the Royal College of Physicians, based on table 2.3 of the R.C.P. report, are not supported by a re-examination of certain data in the report and by analysis of data that were omitted.

One basic argument of the R.C.P. rests on the assertion that cigarette smoking fell in British doctors without a comparable decline in smoking in the general population. This assertion does not seem true for the period 1961 to 1965, when the per cent decrease of cigarette smokers was about the same in the general population as in the Doll/Hill sample of British doctors.

In addition, the omission of data for the age group 35–84 and for the middle time period (1958–61) has created an erroneous parallelism of falling death-rates and declining cigarette smoking in British doctors. When considered for ages 35–84 rather than 35–64, the death-rates of British doctors did not consistently decline, and for most diseases actually rose rather than fell for the two time periods considered by the R.C.P. When these two time periods are augmented by their middle period (1958–61) the doctors' death-rates showed many inconsistencies.

It might be argued that the benefits derived from stopping cigarette smoking take time to appear, and that the interval from 1953–57 to 1958–61 is too short to show any appreciable reduction in death-rates for certain causes of disease. However, table 25 in Doll and Hill's 1964 report on the British doctors [9] shows that in less than five years after smoking was stopped, the death-rate of former cigarette smokers had fallen by 25% from the level of continuing cigarette smokers (from 7·19 to 5·36 per 1000) for "related diseases" and by 34% for the "unrelated diseases" (from 9·43 to 6·26 per 1000). In interpreting these data, Doll and Hill concluded that "the fall in mortality with the stopping of smoking is a real effect as far as the 'related' diseases are concerned, while for the 'unrelated' diseases it is an artifact due to selection".

Regardless of the reasons for the decline, the mortality-rates of former cigarette smokers seem to decline "immediately" after smoking is given up. Such a decline, however, was not reflected in the mortality-rates for British doctors from the period 1953–57 to 1958–61. On the contrary, from 1953–57 to 1958–61, when the proportion of cigarette smokers dropped sharply, the death-rates of British doctors (ages 35 to 84) showed an increase of 4%, 2%, and 4%, respectively, for "related causes", "unrelated causes", and "all causes", and for ages 35–64 changes of 0%, +1%, and 0%.

A curious feature of Doll and Hill's 1964 report on British doctors is that the death-rates of former cigarette smokers (less than 5 years after stopping smoking) fell more for "unrelated causes" than for "related causes". This inconsistency is also found in R.C.P. table 2.3, where for British doctors the death-rates for "unrelated causes" fell by 17%, compared to a 10% fall for "major diseases related to cigarette smoking".

The absence of data for all adult ages in the R.C.P. report is significant but seems less serious than the omission of the data for the middle time period, 1958–61. Since a consideration of the middle-period data seems to alter the results so distinctly, the omission of this information is unfortunate.

This reappraisal of the full data provides strong support for Bradford Hill's injunction about the hazards of analysing secular changes in death rates. The reappraisal also raises major doubts about the Royal College of Physicians' conclusion that it has presented "the strongest evidence there is of the value of giving up cigarettes".

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Source: https://www.industrydocuments.ucsf.edu/docs/rrlk0000

SMOKING AND HEALTH

SIR,—Dr. Seltzer's article (Jan. 29, p. 243) on the Royal College of Physicians' report on smoking and health is in fact concerned only with one table in the report and the conclusions derived from it that stopping smoking increases life expectation. With this he disagrees. The inadequacy of Dr. Seltzer's arguments are so well presented by your leading article and by Sir Richard Doll (Feb. 5, p. 322) that no more need be said about them, but one error should be corrected. He says that no reason was given for the classification of diseases related and unrelated to cigarette-smoking which was used in the table. If he had read the rest of the report he would have found the explanation in paragraph 6.11. There he would also have found a reference to independent evidence of a favourable trend in coronary deaths among doctors associated with their decline in cigarette-smoking, which he does not consider in his article.

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REPORT ON SMOKING AND HEALTH

SIR,—In your issue of Jan. 29 (p. 243) you published a paper by Dr. Carl C. Seltzer in which he examined some of the data on which the Royal College of Physicians based its conclusions concerning cigarette smoking and health. In an accompanying editorial (p. 238) you expressed considerable criticism of Dr. Seltzer's critique.

The editorial disputed Dr. Seltzer on one main point. The Royal College of Physicians had attached particular importance to the observation that between 1953 and 1965 the mortality in male British doctors, many of whom it was believed had stopped smoking, decreased more rapidly than in all men of the same age in England and Wales, among whom it was believed that smoking habits had remained relatively unchanged. Seltzer objected to the geographical, population, and age restrictions and unexpected changes in classification of disease in the data used by the Royal College, to the omission of crucial time periods, and to the assumption of unverified trends in smoking habits. Seltzer found that, once all the data were included which he considered to be pertinent, differences in mortality trends between former smokers and non-smokers largely disappeared.

Dr. Seltzer's findings also were attacked by Sir Richard Doll (Feb. 5, p. 322), who pointed out that pattern of change in mortality with the length of time that smoking had been stopped varied with the nature of the disease, but that ". . . after smoking had been stopped for ten or more years the mortality from 'related causes' had fallen by 38% . . .".

Now I find it extremely curious that Seltzer's conclusions, disputed in that editorial, had been quietly conceded by others, foremost of whom is Doll. In an analysis of lung-cancer death-rates presented to the Royal Statistical Society—an analysis of the same data on which the R.C.P. has based its report—Doll says: "The impression has, therefore, been gained that the incidence of the disease falls when smoking is stopped. In fact, this is not necessarily so; and the published results are compatible with the decreasing incidence, the constant incidence, or one which rises steadily but less rapidly than in men who continue to smoke." And, on the same page: "The results are compatible with the hypothesis that damage produced by smoking is irreversible and that the risk remains practically the same as it was when smoking was stopped; the trend, however, is smooth and suggests that the risk may fall slightly at first and rise again slowly in keeping with the increase in risk in non-smokers."[4] Here Doll maintained for lung cancer precisely what Seltzer did for all mortality—namely, that when all pertinent time periods are considered, the change in mortality between non-smokers and those who cease smoking differs in no way. Doll used this assertion to support his claims that the damage done by smoking is irreversible. The Royal College (and Doll on other occasions) have given a different slant to the same data.

Your editorial criticised Seltzer also for disputing the belief that since 1960 smoking declined among British doctors but not in the general population. Here, again, we find that Doll, too, reported the disputed decline in cigarette consumption among men in the United Kingdom.[5] According to substantive evidence available for some time then, it would appear that Dr. Seltzer's critique was justified.

The issue of smoking and health calls forth emotional responses of which we all need to beware, since they tend to distort the scientific process. One example of what may happen is the way all parties have ignored the tenuous base of their numbers game. Doll's data on British physicians are based on a self-selected sample of physicians who voluntarily responded to questionaries. 30% of the physicians failed to respond to the original inquiry,[6] and the proportion of respondents has continuously decreased since then with each follow-up attempt. The danger of drawing conclusions from samples with high non-response rates has been generally recognised. Bradford Hill calls a non-response rate of 2 to 3% "satisfactorily small".[7] And, indeed, the characteristics of responding physicians are reported to be quite different from those of the general population.[8] As a result, any differences between observations on volunteering physicians and on census populations are difficult to interpret. In addition, estimates of smoking rates are uncertain in the extreme. Estimates of the smoking habits of the same population by use of similar methods may differ by more than a third for some age-groups.[9] From data with all these shortcomings, not much can be learned.

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SMOKING AND HEALTH

SIR,—Your editorial accompanying my article of Jan. 29 (p. 243) offered some apparent justification for the omission of data in the Royal College of Physicians' (R.C.P.) report on smoking and health [1] and raised a question about my own sources of data. I should like to comment on the points raised.

(1) The R.C.P. analysed data for ages 35–64. The analysis did not include data for ages 65–84 or the total results for ages 35–84. You imply that the missing data were not important, because of an allegedly lesser smoking effect in older age-groups. Nevertheless, your conclusions (and those in the R.C.P. report) referred to general effects of stopping smoking; not to any one age-group. Since the trends cited by the R.C.P. for ages 35–64 become reversed or distinctly muted when the data are examined for ages 35–84, this additional information warranted inclusion in the report. The extrapolation of the conclusion to all age-groups certainly seems inappropriate.

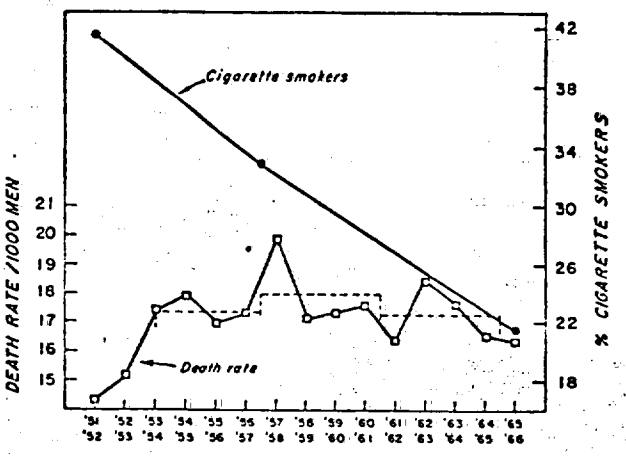
(2) The trends reported by R.C.P. were obtained by a comparison of data for 1953–57 and 1962–65. A straight line can always be drawn between two points, but the validity of the trend is enhanced if at least three points fit the line. The R.C.P. report did not include data for such a third point—the intermediate time period 1958–61. When data for the missing "middle point" are included many of the apparent trends vanish or are substantially altered. You justify the omission of this important middle time period by stating that the main effects of stopping smoking, although observed "surprisingly quickly", are seen more clearly 5–10 years later. If this statement is correct, the trends noted from the first to the intermediate time period should follow the same direction as the trends noted between the intermediate and later time period. For many of the cited diseases, however, the R.C.P. data do not confirm this expectation. In coronary heart-disease, for example, the downward trend at ages 35–64 from 1953–57 to 1958–61 is reversed to a slight upward trend from 1958–61 to 1962–65.

(3) The report's claims rest on the statement that during the cited time periods, cigarette smoking declined among British doctors but not in the general population. In my paper I pointed out the inaccuracy of this statement, and noted that from 1961 to 1965 the percentage of cigarette smokers decreased at about the same rate in men of both the medical and general populations. This same observation (of a decline in cigarette smokers after 1960) was made by Doll in his fig. 3 and text of a previous report [2]: "... the per caput consumption of cigarettes ... in men ... began to fall [after 1960]".

You question the source of my data about cigarette smoking. The data for the British doctors came from the R.C.P. report.[1] The data for the U.K. general population came from the same source [3] used by Doll.[2] To convert the original citations into the reported data, I used certain computations that were not published. The details of these computations for the years 1956, 1961, and 1965 are as follows:

Computations of 1956 cigarette smokers only figure of 56%.—Table 7 of the 1957 T.R.C. report [3] gives the % of men for 1956 ages 35–69 smoking packeted cigarettes only as 52·3%, hand-rolled only as 5·7%, hand-rolled and packeted cigarettes as 3·1%, making a total of 61·1%. The % of men ages 60+ smoking packeted cigarettes only is given as 33·3%, hand-rolled only as 6·7%, hand-rolled and packeted cigarettes as 1·7%, making a total of 41·7%. The U.K. adult male 1956 population was 7,473,000 for ages 35–59 and 3,020,000 for ages 60+. To compute % of cigarette smokers only for ages 35+ take 61·1% of 7,473,000 and add 41·7% of 3,020,000 and divide by total population 10,493,000 × 100 = 56%.

Computations of 1961 cigarette smokers only figure of 57%.—Table 12 of the 1969 T.R.C. report [3] gives the number of cigarette smokers only for men for 1961 ages 35+ as 7,120,000 and the total number of smokers for men ages 35+ as 9,220,000. Therefore, percentage of cigarette only smokers as a proportion of all smokers ages 35+ = 7,120,000/9,220,000 or 77%. Table 11a of the 1969 T.R.C. report gives the % of male non-smokers (including ex-smokers) ages 35–59 as 25% (base 1992) and for ages 60+ as 29% (base 789). Therefore, % non-smokers ages 35+ = 25 × 1992 + 29 × 789/2781 = 26%. Percentage of smokers ages 35+ is accordingly 74% (100 − 26). % of cigarette smokers only is 77% of 74%, or 57%.



Secular trends in death-rates and percentage cigarette smokers for British doctors ages 35 to 84 from 1951 to 1966 (standardised for age).

Death-rates taken from table 1 and percentage cigarette smokers from table 4 of Doll and Pike.[3] The dashed lines (semi-bar graphs) show average death-rate values for the periods 1953–57, 1957–61, and 1961–65 as given in table 2 of Doll and Pike.[3]

Computations of 1965 cigarette smokers only figure of 46%.—Table 12 of the 1969 T.R.C. report gives the number of cigarette smokers only for men for 1965 ages 35+ as 5,891,000 and the total number of men smokers ages 35+ as 8,877,000. Therefore, the % of cigarette only smokers as a proportion of all smokers ages 35+ = 5,891,000/8,877,000 or 66%. Table 11a of the T.R.C. report gives the % non-smokers (including ex-smokers) ages 35–59 as 29% (base 1618) and for ages 60+ as 31% (base 720). Therefore, % non-smokers ages 35+ = 29 × 1618 + 31 × 720/2338 = 30%. Percentage of smokers ages 35+ is accordingly 70% (100 − 30). % of cigarette smokers only is 66% of 70%, or 46%.

The results pertain only to the percentage of cigarette smokers, and data were not available for the years before 1956. For the crucial time period between 1961 and 1965 (not the earlier period, as asserted in your editorial), cigarette smoking declined in the general population, although the overall death-rate remained essentially the same. You did not comment on this crucial phenomenon, despite the doubt it raises for the claim that death-rate is reduced by stopping smoking.

Your statement that the "overall consumption of tobacco in the country as a whole has changed very little" is curious. The data to support this statement are attributed to a paper by Doll and Pike [3] and indicate that the average number of cigarettes smoked per day by all adult males in the U.K. was 11·0 for 1951, 11·5 for 1957, and 11·4 for 1966. However, you omit some important intermediate time periods. By computations from the same source [3] used by Doll and Pike, I have found that the comparable figures were 12·5 for 1961 and 11·4 for 1965, thus confirming that a decline in cigarette smoking occurred from 1961 to 1965. Since Doll had previously [2] acknowledged the reduction in the general population's cigarette smoking after 1960, you have placed Doll in the position of contradicting himself.

Your editorial attributed to the paper by Doll and Pike [3] figures of the average numbers of cigarettes smoked per day by doctors (ages 35–61) as 10·8, 8·3, and 5·5 for the years 1951, 1957, and 1966, respectively. But Doll and Pike's paper does not contain such data.

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(4) A final point that can be noted in the recent Doll and Pike report [5] is the relationship between death-rate and a reduction in cigarette smoking among British doctors. From tables 1, 2, and 4 of that report, I constructed the accompanying figure. The years 1951–52 and 1952–53 are omitted because of Doll and Pike's suggestion [5] that the mortality-rates in those years are "obviously biased" by the way the cohort of British doctors was selected. The graph shows no correspondence between the death-rates among British doctors from 1953 to 1965, and their simultaneous downward trend in cigarette smoking.

These data from the Doll and Pike report provide perhaps the most vigorous refutation yet offered for the conclusion in your editorial and in the R.C.P. report that "changes in mortality among British doctors provide strong evidence that stopping smoking increases the expectation of life".

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SMOKING AND HEALTH

SIR,—Are we to judge from their silence that Dr. Seltzer's critics have conceded his case (Jan. 29, p. 243, and March 11, p. 586)? Is cigarette-smoking non-lethal?

If the undoubted positive associations between cigarette smoking and death-rates from various diseases are not causal in origin, an alternative explanation is needed. According to Fisher,[1] such associations might arise from constitutional factors. That is to say, one or more of the genes that predispose to certain forms of smoking might be the same as, or linked with, genes that predispose to fatal disorders such as lung cancer. In principle, we can discriminate between causal and constitutional hypotheses by examining deaths in series of twins discordant for smoking habits. The straightforward causal hypothesis predicts that deaths will occur earlier, on the average, in the smoking members of both monozygotic and dizygotic twin pairs. The constitutional hypothesis predicts that "early deaths" will occur with equal frequency, on the average, among the smoking and the non-smoking members of monozygotic twin pairs: where dizygotic twins are concerned, smokers should suffer an excess frequency of "early deaths" over non-smokers.

This simple test of the two hypotheses is, of course, hindered by the rarity of monozygotic twins discordant for smoking habits: only some 20–25% have been found to be strikingly discordant.[1,2]

Despite this obstacle, Friberg et al.[3] have obtained some intriguing results. They studied deaths among 246 male and 326 female monozygotic twin pairs, and in 706 male and 781 female dizygotic twin pairs appreciably discordant ("non-smoker" versus "smoker"; "less exposed" versus "more exposed"), and born in Sweden between 1901 and 1925. Among the dizygotic male twins, deaths were recorded over a standard period as follows: 13 of the "non-exposed and less-exposed" as compared with 34 of the "smoker and more exposed". Among dizygotic female pairs, deaths were recorded in 18 of the "non-exposed and less-exposed" and 20 of the "smoker and more exposed". Results for discordant monozygotic twins were very interesting: 14 deaths were recorded among the "non-exposed and less-exposed" men, but only 9 among the "smokers and more exposed"; among the women, 4 of the "non-exposed and less-exposed" and 6 of the "smoker and more exposed" died. Overall, the "more exposed" (sexes combined) enjoyed a slight but not significant advantage (18/15) over the "non-exposed and less-exposed". On a formal statistical test, the difference in mortality ratios ("non-exposed and less-exposed"/"smoker and more exposed") between the sets of monozygotic and dizygotic male twins corroborates the constitutional hypothesis and rejects (at the 1–2% level) the causal hypothesis (x^2 with Yates' correction = 5·78; $0{\cdot}01 < P < 0{\cdot}02$). However, this result needs to be treated with caution because the degree of discordance for smoking habits between the monozygotic and dizygotic series, although similar, was probably not identical. This reservation apart, the independent findings of Friberg et al.[3] support Dr. Seltzer.

Perhaps the issue could be put beyond reasonable doubt by supplementing the study of Friberg and his colleagues [3] with a world-wide survey under the ægis, say, of the World Health Organisation? And why should not the cigarette manufacturers foot the bill?

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1005050725

SMOKING AND HEALTH

SIR,—Professor Burch (June 10, p. 1283) would not have felt that critics of Dr. Seltzer's comments (Jan. 29, p. 243) on evidence concerning changes in mortality-rates of doctors and other men in England and Wales have been silent if he had given more weight to the leading article which you published in the same number as Dr. Seltzer's article (p. 238). Dr. Seltzer's letter (March 11, p. 586) was based on death-rates at all ages and was thus irrelevant to an argument based on changes in death-rates at ages at which stopping smoking could be expected to affect mortality, and thus required no answer. The observations of Friberg et al., which Professor Burch finds so impressive, are very interesting. Since these are based on a very small number of deaths and are in conflict with such a vast array of contrary evidence, it would be unwise to conclude that this evidence alone is valid and all the rest is invalid. If Professor Burch is unaware of other evidence about the constitutional hypothesis, he will find simple statements about it in the Royal College of Physicians' report [1] and more detailed reviews in the Surgeon-General's publications (The Health Consequences of Smoking)—in particular the recent 1971 and 1972 editions.[2,3] I agree with Professor Burch's suggestion that there should be more extensive surveys of mortality in twins with contrasting smoking habits. The difficulty is that these would have to be very large studies, because identical twins tend to have such similar smoking habits that pairs with widely contrasting smoking habits form a very small proportion of the total.

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SMOKING AND HEALTH

SIR,—In your issue of April 29 (p. 960) you published a letter from Dr. Theodore Sterling, of the Department of Applied Mathematics and Computer Science, Washington University, in which he quoted extensively from my articles. According to Sterling the excerpts selected lent support to Seltzer's conclusion (p. 243) that a proper analysis would not show any appreciable difference between the trends in mortality of doctors—many of whom have stopped smoking—and men of the same ages in England and Wales whose smoking habits have remained relatively unchanged. I cannot agree with this contention.

In a letter to *The Lancet* on Feb. 8 (p. 322) I pointed out that the trend of mortality with time after smoking is stopped varies with the nature of the disease, and that in the doctors we had studied the mortality from illnesses related to smoking fell by 38% after 10 or more years. This, Sterling asserts, is contradicted by another statement that after smoking is stopped the incidence of lung cancer remains practically the same as it was at the time of stopping.[1] The reason for the apparent contradiction would not be obvious to anyone who read only these selected statements. It should, however, have been obvious to a mathematician who read them in the context in which they were written. The first statement referred to mortality-rates standardised for age; that is, it compared mortality among men of the same ages. The second referred to the change in the incidence of disease with the passage of time; that is, it compared incidence among men of different ages. Since lung cancer and other diseases related to smoking increase in incidence with age, the two statements are perfectly compatible, and the assertion that Seltzer's conclusion (v.s.) "had been quietly conceded by others, foremost of whom is Doll," is false.

Sterling then quoted me as having reported a decline in cigarette consumption among men in the United Kingdom[2]; which, he said, again supported Seltzer and contradicted your editorial (p. 238). In fact what your editorial said was that the consumption of cigarettes had declined more in doctors than in other men. Nothing I have written contradicts that. No-one disputes the fact that the amount of tobacco smoked by men in Britain has declined since 1960 largely as a result of the introduction of filter-tipped cigarettes. The figures have been published by the Tobacco Research Council and are there for everyone to see,[3] and it is interesting to observe that the mortality from lung cancer in Britain has declined in men under 55 years of age while it has continued to increase at all ages in women, among whom tobacco consumption has continued to increase.

Finally, Sterling refers to the fact that some 30% of the doctors to whom Bradford Hill and I wrote failed to reply, and uses it to cast doubt on the validity of the comparison between the trend in the mortality of those doctors who did reply and the trend in the general population.

The failure to obtain a reply from a substantial proportion of the doctors to whom we originally wrote makes it dangerous to generalise from the respondents to doctors as a whole, as we have repeatedly pointed out.[4] We showed that the doctors who did reply were somewhat healthier than average, so that the mortality-rates among them were at first abnormally low.[4] This bias, however, had largely worn off after 2 years, so that we needed to exclude the first two years' observations from our comparison of trends. From then on the relevant fact is that we were able to keep 99·9% of the doctors under observation for the succeeding 12 years. Doubtless better material could be collected, but I am not convinced that the shortcomings of ours are so great that "not much can be learned" from it.

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Coronary Heart Disease Morbidity

Tables 4 and 5 list the prospective studies carried out in a number of countries to identify the risk of CHD morbidity incurred by smoking. Here, CHD morbidity includes myocardial infarction as well as angina pectoris. Certain studies, notably those of Doyle, et al. (54), Keys, et al. (111), and Taylor, et al. (183) include a number of CHD deaths in their data that could not be separated out using the information provided in their respective reports. As noted in the discussion on CHD mortality, the CHD risk ratio increases significantly as the number of cigarettes smoked per day increases. Similarly, the HIP data of Shapiro, et al. (172) show that the elevated morbidity ratios declined with increasing age as has been shown for mortality ratios.

A recent monograph edited by Keys (111) dealt with the 5-year CHD incidence in males age 40 to 59 from seven countries. As summarized in table 4, cigarette smoking was found to be associated with an increased incidence of CHD in the U.S. railroad worker population, 2,571 individuals (183). None of the differences in ratio between smokers and nonsmokers was statistically significant for the 13 other population samples which varied in size from 605 to 982 individuals, from the five other countries. (Smoking was not considered in the two Japanese populations.) When more cases become available to provide greater statistical stability to the rates, this intercultural comparison should prove illuminating.

The results of those studies which have separated out angina pectoris as a manifestation of CHD are presented in table 5. Doyle, et al. (54) found no relationship between this manifestation of CHD and cigarette smoking. Both Jenkins, et al. (90) and Kannel, et al. (94) observed increased risk ratios among male cigarette smokers although these differences were not statistically significant. More recently, Shapiro, et al. (172) found a significantly increased risk for angina among their male cigarette smokers as well as increasing risk ratios with increasing dosage among both males and females, particularly in the younger age groups. A variety of hypothetical explanations have been advanced to account for this seeming contradiction. Among these are the relatively small number of cases, the difficulties associated with the definitive diagnosis of the syndrome, and differences in the methods of classifying those cases of angina pectoris which are followed by myocardial infarction.

Retrospective Studies

Table A6 presents data from the various retrospective studies of CHD prevalence. Most of these are case-control studies and show an increased percentage of smokers among those with clinical CHD when compared with a selected control population, usually without apparent CHD. Two of these studies include data on mortality.

The Interaction of Cigarette Smoking and Other CHD Risk Factors

The preceding section has reviewed the epidemiologic evidence which supports the judgment that cigarette smoking is a significant risk factor in the development of CHD. Many of the studies discussed above have identified a number of biochemical, physiological, and environmental factors, other than cigarette smoking, which also increase the risk of developing CHD. These risk factors include elevated serum lipids (particularly serum cholesterol) and hypertension, which, with cigarette smoking, are considered to be of greatest importance. Other factors are obesity, physical inactivity, elevated resting heart rate, diabetes (as well as asymptomatic hyperglycemia), electrocardiographic abnormalities, and a positive family history of premature CHD (88).

A number of these studies have also found that these factors, when present in the same individual, exert a combined effect on the risk of developing CHD. Figures 1 through 3 depict this interaction of risk factors. As may be noted in Figures 1 and 2, the additional factor of smoking greatly increases the risk of developing CHD among those people already at high risk because of other factors.

Furthermore, these studies have shown that the effect of smoking on the risk of developing CHD is statistically independent of the other risk factors. That is, when the effect of the other factors is statistically controlled, smoking continues to exert a significant effect on increasing the risk of developing and dying from CHD.

(111) Keys, A. (Editor). Coronary Heart Disease in Seven Countries. Circulation 41(4, Supplement 1): 1970. 211 pp.

(183) Taylor, H. L.; Blackburn, H., Keys, A., Parlin, R. W., Vasquez, C., Puchner, T. Five-year follow-up of employees of selected U.S. railroad companies. IN: Keys, A. (Editor). Coronary Heart Disease in Seven Countries. American Heart Association Monograph No. 2. 1970. pp. 20–39.

172 Shapiro, S., Weinblatt, E., Frank, C. W., Sager, R. V. Incidence of Coronary Heart Disease in a Population Insured for Medical Care (HIP). Myocardial infarction, angina pectoris, and possible myocardial infarction. American Journal of Public Health and the Nation's Health 59(6): Supplement to June 1969. 101 pp.

(90) Jenkins, C. D., Rosenman, R. H., Zyzanski, S. J. Cigarette smoking. Its relationship to coronary heart disease and related risk factors in the Western Collaborative Group Study. Circulation 38(6): 1142–1155, December 1968.

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Smoking and Serum Lipids

The interaction of smoking and serum lipid levels in the development of CHD should be considered in the light of information concerning the relationship of smoking to serum lipid levels. Table A7 presents studies which deal with the association between smoking and lipids, notably cholesterol, triglycerides, and lipoproteins (concerned with lipid transport). While some of the studies have indicated that smokers show increased serum levels of these lipid constituents, others have not. The populations investigated and the methods of the various studies show significant variation. This lack of comparability makes interpretation of the findings difficult.

It is clear, however, that in the presence of high serum cholesterol, cigarette smoking increases the risk of CHD. Figure 4 depicts the data from the Chicago Peoples Gas, Light and Coke Company study which show that smoking greatly increases the risk of CHD in each of the cholesterol groups.

Smoking and Hypertension

Some epidemiological studies have indicated that smokers tend to have lower mean systolic and/or diastolic blood pressures than nonsmokers, while other studies have not found this to be the case (table A8). Reid, et al. (*155*), in a study of 1,300 British and American postal workers, found that the blood pressure difference between the smoking and nonsmoking groups was eliminated after controlling for body weight.

Tables 9 through 11, derived from the study by Borhani, et al. (*27*), demonstrate the following associations: That for both smokers and nonsmokers, the risk of dying from CHD increases with increasing diastolic or systolic pressure, and that the risk of mortality from CHD is higher among smokers than among nonsmokers in each blood pressure group. Cigarette smoking, therefore, has been shown to elevate CHD mortality independently both of its effect on blood pressure and of the effect of hypertension on CHD.

Smoking and Physical Inactivity

The recent study by Shapiro, et al. (*172*) of more than 110,000 persons participating in the Health Insurance Plan of New York City has further identified and elaborated upon the interaction of the various risk factors. Physical inactivity, both in employment and during leisure time, was found to be a potent risk factor for the development of CHD, particularly for rapidly fatal myocardial infarction.

Figure 5 depicts the effect which smoking exerts on CHD in combination with physical inactivity. Of note, also, is the observation that within each activity grouping, smoking greatly increases the risk of myocardial infarction, thus exerting an independent effect.

Smoking and Obesity

The analysis by Truett, et al. (*190*) of the risk factor data from the Framingham study revealed that weight, while a significant risk factor, had a considerably smaller effect on CHD incidence than serum cholesterol, cigarette smoking, or elevated blood pressure. The results concerning the interaction of smoking and obesity from the San Francisco longshoremen study are shown in table 12.

(155) Reid, D. D., Holland, W. W., Rose, G. A. An Anglo-American cardiovascular comparison. Lancet 2(7531): 1375–1378, December 30, 1967.

(27) Borhani, N. O., Hechter, H. H., Breslow, L. Report of a 10-year follow-up study of the San Francisco longshoremen. Mortality from coronary heart disease and from all causes. Journal of Chronic Diseases 16: 1251–1266, 1963.

(190) Truett, J., Cornfield, J., Kannel, W. A multivariate analysis of the risk of coronary heart disease in Framingham. Journal of Chronic Diseases 20: 511–524, 1967.

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Source: https://www.industrydocuments.ucsf.edu/docs/mk0000

TABLE 9.—*Death rates from coronary heart disease, by systolic blood pressure: ILWU mortality study 1951–61*
(Coronary heart disease as classified under ISC Code 420)

Age group	Systolic blood pressure in 1951	Smokers: Person-years of observation	Smokers: Death rate[1]	Nonsmokers: Person-years of observation	Nonsmokers: Death rate[1]
45–64	<130	1,577	27	2,413	8
	130–149	2,036	84	2,912	17
	150–169	749	95	1,177	26
	>170	369	109	672	45
65–64	<130	1,057	84	1,550	[2]6
	130–149	1,380	94	2,401	[2]25
	150–169	647	93	1,558	45
	>170	524	210	1,117	125

[1] Rate per 10,000 person-years of observation.
[2] $p<0.025$.
[3] $p<0.01$.
SOURCE: Borhani, N. O., et al. (27).

TABLE 10.—*Death rates from coronary heart disease, by diastolic blood pressure: ILWU mortality study, 1951–61*
(Coronary heart disease as classified under ISC Code 420)

Age group	Diastolic blood pressure in 1951	Smokers: Person-years of observation	Smokers: Death rate[1]	Nonsmokers: Person-years of observation	Nonsmokers: Death rate[1]
45–64	<80	1,527	26	1,700	6
	80– 89	2,115	47	2,947	17
	90– 99	951	52	1,507	33
	>100	449	89	1,020	20
65–64	<80	1,059	104	1,447	[2]21
	80– 89	1,521	89	2,704	15
	90– 99	869	194	1,521	[2]48
	>100	369	163	954	147

[1] Rate per 10,000 person-years of observation.
[2] $p<0.05$.
[3] $p<0.01$.
SOURCE: Borhani, N. O., et al. (27).

TABLE 11.—*Death rates from coronary heart disease, among hypertensives and nonhypertensives: ILWU mortality study, 1951–61*
(Coronary heart disease as classified under ISC Code 420)

Age group	Blood pressure status[1]	Smokers: Person-years of observation	Smokers: Death rate[2]	Nonsmokers: Person-years of observation	Nonsmokers: Death rate[2]
45–64	Hypertensives	883	125	1,871	[3]32
	Nonhypertensives	4,169	29	5,303	13
65–64	Hypertensives	931	180	2,219	95
	Nonhypertensives	2,657	93	4,407	[3]16

[1] According to the WHO recommendation, the following cut-off points are recommended for the definition of hypertension:
(1) Normotension—below 140/90 mm. Hg.
(2) Hypertension—systolic blood pressure 160 mm. Hg. or over, or diastolic 95 mm. Hg. or over, or both.
(3) Borderline—the residual category. In this analysis, Normotensives and Borderlines were combined and the population was grouped into 'Nonhypertensives' (1 and 3) and 'Hypertensives' (2).
[2] Rate per 10,000 person-years of observation.
[3] $p<0.01$.
SOURCE: Borhani, N. O., et al. (27).

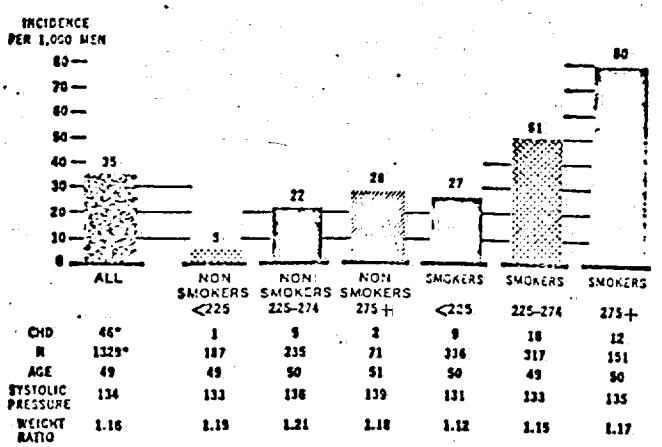

FIGURE 4—Relationship between smoking status and serum cholesterol level at initial examination, and incidence of clinical coronary heart disease in men originally age 40–59, free of definite CHD, and followed subsequently without systematic intervention, Peoples Gas Light and Coke Company study, 1958–1962. *For 34 men, no information on smoking status was available; one of these men had a coronary episode.
SOURCE: Stamler, J., et al. (177).

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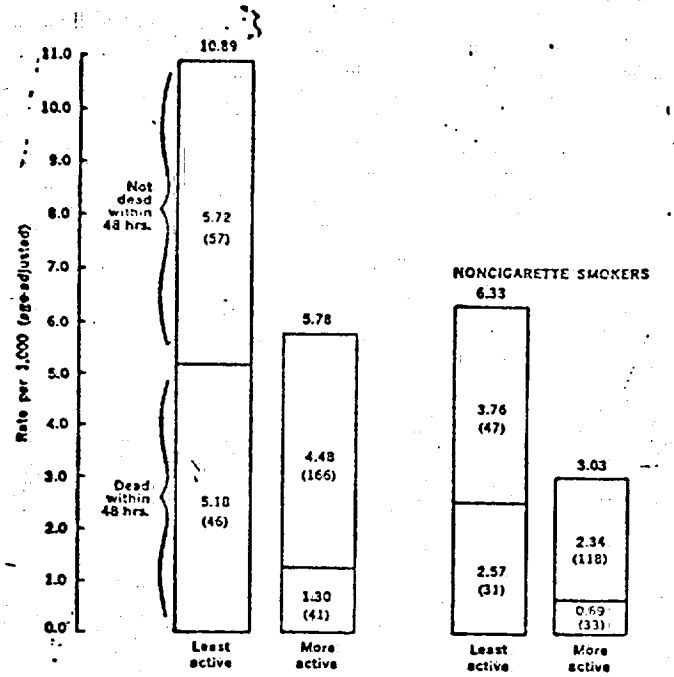

Note: Both for cigarette smokers and noncigarette smokers differences between rates among the least and more active men are statistically significant for total MI and rapidly fatal MIs at the 0.99 confidence level. For other MIs the difference is statistically significant only for the nonsmokers (confidence level 0.95).

FIGURE 5—Average annual incidence of first myocardial infarction among men in relation to overall physical activity class and smoking habits (age-adjusted rates per 1,000)

(Actual number of deaths or myocardial infarctions are represented by figures in parentheses)

SOURCE: Shapiro, S., et al. (*172*).

This table shows that cigarette smokers in the 55 to 64 year age group were observed to have higher CHD death rates than nonsmokers in all weight categories. Similar findings, although not in all weight groups, were observed for the 45 to 54 year age group. Cigarette smoking is thus shown to be a CHD risk factor independent of body weight.

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Smoking and Electrocardiographic Abnormalities

Electrocardiographic (ECG) abnormalities such as T-wave and ST-segment changes as well as a number of arrhythmias are useful indicators of CHD and may, therefore, be predictive of the development of clinically overt CHD manifestations. The results summarized in table 13, from the prospective study by Borhani, et al. (*27*), reflect the joint predictive value of smoking and ECG abnormalities on the death rate from CHD.

Smoking and Heart Rate

Recent analysis by Berkson, et al. (*23*) of the data derived from the Chicago Peoples Gas, Light and Coke Company study of middle-aged men revealed that resting heart rates of 80 or greater were associated with an increase in the risk of death from CHD. These authors found that this association was independent of the other major coronary risk factors.

Table 14 presents the interaction between smoking, blood pressure, and elevated heart rate in increasing the risk of CHD mortality. This study shows that cigarette smoking increases CHD risk in the presence of elevated heart rate as well as in its absence.

(*23*) BERKSON, D. M., STAMLER, J. LINDBERG, H. A., MILLER, W. A., STEVENS, E. L., SOYUCENIC, R., TOKICH, T. J., STAMLER, R. Heart rate: An important risk factor for coronary mortality—ten-year experience of the Peoples Gas Co. Epidemiologic study (1958–68). IN: Jones, R. J. (Editor). Atherosclerosis. Proceedings of the Second International Symposium. New York, Springer-Verlag, 1970. pp. 382–389.

Source: https://www.industrydocuments.ucsf.edu/docs/rnk0000

TABLE 12.—*Death rates from coronary heart disease among men without abnormalities related to cardiopulmonary diseases by weight classification in 1951: ILWU mortality study, 1951–61*

(Coronary heart disease as classified under ISC Code 420)

Age group	Weight classification [1]	Smokers		Nonsmokers	
		Person-years of observation	Death rate [2]	Person-years of observation	Death rate [2]
45–54	Not overweight	385	21	279	7
	Slightly overweight	962	28	1,036	0
	Moderately overweight	1,333	25	1,574	25
	Markedly overweight	1,055	22	1,797	0
55–64	Not overweight	222	42	247	0
	Slightly overweight	536	75	605	26
	Moderately overweight	855	109	1,320	[3]11
	Markedly overweight	736	68	1,653	[3]12

[1] The four classes are defined in the text.
[2] Rate per 10,000 person-years of observation.
[3] $p<0.01$.
SOURCE: Borhani, N. O., et al. (27).

TABLE 13.—*Death rates from coronary heart disease, by electrocardiographic findings in 1951: ILWU mortality study, 1951–61*

(Coronary heart disease as classified under ISC Code 420)

Age group	Electrocardiographic findings in 1951	Smokers		Nonsmokers	
		Person-years of observation	Death rate [1]	Person-years of observation	Death rate [1]
45–54	Abnormal	586	102	1,020	39
	Normal	4,454	38	6,134	15
55–64	Abnormal	583	223	1,149	96
	Normal	3,031	88	5,479	[2]31

[1] Rate per 10,000 person-years of observation.
[2] $p<0.025$.
SOURCE: Borhani, N. O., et al. (27).

TABLE 14.—*1958 status with respect to heart rate, blood pressure, cigarette smoking, and 10-year mortality rates, by cause (1,329 men originally age 40–59 and free of definite coronary heart disease) Peoples Gas Co. Study, 1958–68*

1958 risk factor status				Ten-year mortality, 1958–68			
				All causes		CHD	
Heart rate	Cigarette smoking	Diastolic pressure	Number of men	Number	Rate	Number	Rate
NH	NH	NH	378	20	[1]48.3	5	[1]12.0
H	NH	NH	45	6	114.9	3	70.3
NH	NH	H	107	14	118.3	6	51.8
H	NH	H	30	8	221.6	3	82.0
NH	H	NH	491	57	115.2	19	36.9
H	H	NH	127	22	171.1	8	62.3
NH	H	H	103	22	190.4	6	55.0
H	H	H	44	13	265.4	5	94.9
All			[2]1,325	162	113.2	65	39.4

[1] Rate per thousand. All rates are age-adjusted by 5-year age groups to U.S. male population, 1960. High (H): Heart rate ≧80; ≧10 cigarettes per day; diastolic blood pressure ≧90 mm. Hg. NH is not high, i.e., below specified cutting points.
[2] No smoking data available on 4 of the 1,329 men.
SOURCE: Berkson, D. M., et al. (28).

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TABLE 15.—*The effect of the cessation of cigarette smoking on the incidence of CHD*

(Incidence ratios—actual number of cases or events are shown in parentheses)

Author, year, country, reference	Results		Comments
	All CHD events	*All myocardial infarction*	
Jenkins et al., 1968, U.S.A. (90).	Never smoked 1.00 (38)	1.00 (21)	
	Current cigarette smokers 2.35 (84)	2.79 (63)	
	Former cigarette smokers 2.16 (19)	2.47 (15)	
	Death from CHD		
	Smoked 1–19 cigarettes/day	*Smoked >19 cigarettes/day*	
Hammond and Garfinkel, 1969, U.S.A. (76).	Never smoked regularly 1.00 (1,341)	1.00 (1,341)	Male data only
	Current cigarette smokers 1.30 (1,065)	2.55 (2,972)	
	Stopped <1 year 1.42 (29)	1.81 (62)	
	1–4 ..... 1.22 (57)	1.51 (158)	
	5–9 ..... 1.26 (63)	1.18 (135)	
	10–19 ..... 0.98 (63)	1.25 (135)	
	>20 ..... 1.03 (70)	1.05 (101)	
	All ex-cigarette smokers .. 1.16 (263)	1.25 (564)	
	Total definite myocardial infarction		
Shapiro et al., 1968, U.S.A. (172).	Never smoked 1.00		
	Current cigarette smokers 1.81		
	Stopped ≤5 years 0.76		
	All CHD deaths	*First major coronary event*	
Pooling Project, American Heart Association 1970, U.S.A. (84).	Never smoked 1.00 (27)	1.00 (33)	See table 4 for description of Pooling Project.
	>½ pack/day 1.65 (34)	1.65 (72)	
	1 pack/day 1.70 (86)	2.88 (205)	
	>1 pack/day 3.00 (45)	3.25 (154)	
	Ex-smokers 0.80 (19)	1.28 (61)	

TABLE 16.—*Annual probability of death from coronary heart disease, for current and discontinued smokers, by age, maximum amount smoked, and age started smoking*

Age	Maximum daily number of cigarettes smoked	Age started smoking: 15–19 — Current smokers	15–19 — Discontinued for five or more years (Probability X10⁴)	20–24 — Current smokers	20–24 — Discontinued for five or more years
55–64	0	691	—	691	—
	10–20	798	668	811	651
	21–39	869	764	872	698
65–74[1]	0	1,016	—	1,015	—
	10–20	1,501	1,169	1,478	1,213
	21–39	1,518	1,334	1,573	1,098

[1] For age group 65–74, probabilities for discontinued smokers are for 10 or more years of discontinuance since data for the 5–9 year discontinuance group are not given.

SOURCE: Cornfield, J., Mitchell, S. (45).
Based on data derived from Kahn, H. A. (93).

THE EFFECT OF CESSATION OF CIGARETTE SMOKING ON CORONARY HEART DISEASE

A number of epidemiological studies have been concerned with the CHD incidence and mortality among ex-cigarette smokers as compared with current smokers (*51, 76, 88, 90, 93, 172*). These studies are listed in table 15. Table 16 presents the data derived by Cornfield and Mitchell (*45*) from the Dorn Study of U.S. Veterans (*93*).

Ex-cigarette smokers show a reduced risk of both myocardial infarction and death from CHD relative to that of continuing cigarette smokers. The Pooling Project (*33*) and the Western Collaborative Study Group (*192*) which adjusted for the other risk factors of elevated serum cholesterol and blood pressure observed this relationship. Hammond and Garfinkel (*76*) noted that cessation of smoking is accompanied by a relative decrease in risk of death from CHD within 1 year after stopping.

This decreased risk of CHD among ex-smokers further strengthens the relationship between smoking and CHD. It must be noted, however, that the group of ex-smokers is composed of individuals who have stopped smoking for a variety of reasons. Those who stop because of ill health and the presence of symptoms are generally at high risk and can bias the group results in one direction; those healthy persons who stop as part of a general concern about their health and may adopt a number of self-protective health practices are generally at low risk and can bias the group results in the other direction. Therefore, ex-smokers as a group are not fully representative of the entire population of smokers and may have limited value in predicting what would happen if large numbers of cigarette smokers stopped smoking purely for self-protection. Certain incidence studies, such as the Pooling Project (*33*), were initiated with only clinically healthy individuals. The data from such studies, as well as those from the British physicians study, contain ex-smoker data less influenced by these biases.

(45) CORNFIELD, J., MITCHELL, S. Selected risk factors in coronary disease: Possible intervention effects. Archives of Environmental Health 19(3): 382–394, September 1969.

(51) DOLL, R., HILL, A. B. Mortality in relation to smoking: 10 years' observations of British doctors. (Concluded) British Medical Journal 1(5396): 1460–1467. June 6. 1964.

(76) HAMMOND, E. C., GARFINKEL, L. Coronary heart disease, stroke, and aortic aneurysm. Factors in the etiology. Archives of Environmental Health 19(2): 167–182, August 1969.

(192) U.S. PUBLIC HEALTH SERVICE. The Health Consequences of Smoking. 1968 Supplement to the 1967 Public Health Service Review. Washington, U.S. Department of Health, Education, and Welfare, Public Health Service Publication No. 1696, 1968. 117 pp.

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Fletcher and Horn (*63*) have recently presented data derived from the British physicians study of Doll and Hill. Over the past 10-15 years, cigarette smoking rates among British physicians have declined significantly in comparison with those of the general British population. The information presented by these authors concerning all cardiovascular diseases showed that for individuals between the ages of 35 and 64, the age-adjusted death rate for CHD declined by 6 percent among physicians and rose by 10 percent among the male population of England and Wales during the period from 1953–57 to 1961–65.

(*63*) FLETCHER, C. M., HORN, D. Smoking and health. WHO Chronicle 24(8): 345–370, August 1970.

THE CONSTITUTIONAL HYPOTHESIS

The effect of smoking on the incidence of CHD has been found to be independent of the influence of the other CHD risk factors. When such risk factors as high serum cholesterol (*177*), increased blood pressure (*27*), elevated resting heart rate (*23*), physical inactivity (*172*), obesity (*27*), and electrocardiographic abnormalities (*27*) have been controlled, cigarette smokers still show higher rates of CHD than nonsmokers.

It has been suggested by some (*39, 170*) that the relationship between cigarette smoking and CHD has a constitutional basis. That is people with certain constitutional make-ups are more likely to develop CHD, and the same people are more likely to smoke cigarettes. This hypothesis maintains that the relationship between cigarette smoking and CHD is thus largely fortuitous and that the significant relationships are between the genetic make-up of the individual and CHD and between the genetic make-up of the individual and his becoming a cigarette smoker. Two sets of epidemiologic data bear on this hypothesis.

It has been maintained that people with a certain temperament are more likely to smoke and also more likely to develop CHD. These characteristics have been demonstrated for those with the Type A behavior pattern of Rosenmann, et al. (*159*) which is characterized by competitiveness, excessive drive, and an enhanced sense of time urgency. The prospective study organized by the Western Collaborative Group indicates that individuals who exhibit this type of personality are more likely to have or develop CHD than those without it (Type B), whether or not they smoke. When the incidence rates of CHD are analyzed with respect to smoking and personality types (tables A17, A18), it is noted that in both Type A and Type B individuals the incidence of CHD is greater among cigarette smokers than among nonsmokers. This research indicates that both personality type, as measured in these studies, and cigarette smoking contribute independently as risk factors to the development of CHD. To what extent such behavior patterns are determined constitutionally or represent acquired characteristics is still open to question.

The other type of research designed to study the genetic hypothesis has made use of data from registries of twins. Cederlof, et al. (*37, 38, 39, 40*) have utilized the Twin Registries of Sweden and the Veterans Follow-Up Agency of the U.S. National Academy of Sciences–National Research Council to investigate the relative contributions of heredity and smoking to cardiovascular and bronchopulmonary symptom prevalence. Data obtained by mailed questionnaires were analyzed for the following characteristics: zygosity of the same-sex twin pair, urban-rural residence differences, smoking concordance, and history of various symptoms. Comparisons were made between smoking discordant monozygotic (identical) pairs and smoking discordant dizygotic (fraternal) pairs, and between unmatched twin pairs and matched twin pairs. Smoking discordance has been defined somewhat differently in various reports but, in general, describes twin pairs in which the smoking habits differ between the two members of the same twin pair.

(*39*) CEDERLOF, R., FRIBERG, L., JONSSON, E., KAIZ, L. Respiratory symptoms and "angina pectoris" in twins with reference to smoking habits. An epidemiological study with mailed questionnaire. Archives of Environmental Health 13 (6): 726–737, December 1966.

(*159*) ROSENMAN, R. H., FRIEDMAN, M., STRAUS, R., WURM, M. KOSITCHEK, R., HAHN, W., WERTHESSEN, N. T. A predictive study of coronary heart disease. The Western Collaborative Group Study. Journal of the American Medical Association 189(1): 15–22, July 6, 1964.

(*37*) CEDERLOF, R. The Twin Method in Epidemiological Studies on Chronic Disease. Institute of Hygiene of the Karolinska Institute, Department of Environmental Hygiene of the National Institute of Public Health, Department of Sociology, University of Stockholm, Stockholm, 1966. 71 pp.

(*38*) CEDERLOF, R., FRIBERG, L., HRUBEC, Z. Cardiovascular and respiratory symptoms in relation to tobacco smoking. A study on American twins. Archives of Environmental Health 18(6): 934–940, June 1969.

(*40*) CEDERLOF, R., JONSSON, E., LUNDMAN, T. On the validity of mailed questionnaires in diagnosing "angina pectoris" and "bronchitis". Archives of Environmental Health 13(6): 738–742, December 1966.

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Analyzing the data obtained from 9,319 Swedish twin pairs (72.3 percent of the possible respondents), Cederlof, et al. (*39*) found that respiratory symptoms were more common among smokers in both the unmatched and matched smoking discordant twin pair groups. The authors analyzed the data in two distinct manners. Group A analysis, which did not control for genetic factors utilized two groups; the first composed of all the firstborn, and the second of those listed second on the birth certificates. Group B analysis utilized MZ and DZ twin pairs which were discordant for smoking, thereby controlling genetic factors. "Angina pectoris," as defined by a certain pattern of responses to the questionnaire, was found to be more prevalent among smokers in Group A, but this difference was not present when the data from Group B were analyzed. Males in the first group exhibited a "hypermorbidity ratio" of 1.6, while those in the second group were found to have one of approximately 1.1. The authors concluded that this difference between the two groups provides better support for the importance of constitutional factors as against the importance of cigarette smoking in the development of angina pectoris.

A similar study was done using the responses of 4,379 U.S. Veteran twin pairs (approximately 60 percent of estimated available total) who completed the mailed questionnaires (*38*). Cederlof, et al. found a significantly increased prevalence of chest pain and "angina pectoris" among smokers when Group A was analyzed. Analysis of the smoking-discordant matched twin pairs (Group B) revealed no association between smoking and cardiovascular symptoms among the monozygotic pairs. The dizygotic pair data did show a slight association. The authors concluded that this lack of association among the monozygotes and its presence among the dizygotes and unmatched pairs strengthens the case for a constitutional hypothesis.

A major problem in these studies is the small number of cases available and, therefore, the statistical instability of the results. In the Swedish study, among the 274 monozygotes, only 19 smokers and 16 nonsmokers were classified as having angina pectoris while among the 733 dizygotes, 25 smokers and 25 nonsmokers were so classified. In neither group was the difference between the prevalence ratios found in the Group A analysis and that in the Group B analysis of statistical significance. Analysis of the data on women shows a similar lack of significance.

Similar criticisms may be made of the study which utilized the U.S. Veteran Twin Registry. In that study, the authors observed that the difference in the prevalence of angina pectoris between the low-cigarette-exposure and high-cigarette-exposure dizygotic groups was not present among the monozygotes. The authors questioned whether the excess morbidity associated with cigarette smoking found in the dizygotic group was causal as it was not possible to reproduce the association when studying monozygotic smoking-discordant twin pairs. As noted above, the numbers in this study are also small so that the differences in rates do not approach statistical significance.

Tibblin (*188*) has questioned the value of a mailed questionnaire to diagnose heart disease. The questionnaire as originally constructed was used and validated by interview technique alone (*157*, *158*). Cederlof, et al. (*40*) conducted a study to determine the validity of this questionnaire as a mailed instrument by personally interviewing and examining 170 of the twin pairs who had replied. Of the eight males who were diagnosed as having "angina pectoris" by the questionnaire, four were found to be free of symptoms on clinical examination, while among 204 responding negatively, two were found to have angina by clinical criteria. None of the 11 women who were diagnosed as positive by questionnaire was found to be clinically affected, and of the 136 reporting as negative, three had symptoms of angina pectoris.

Other major difficulties associated with these studies include the problems of using prevalence data in the investigation of a disease (CHD) from which a significant number of those affected die shortly after the onset of symptoms, the inclusion of ex-smokers in the smoking population, and the low numbers of heavy cigarette smokers in the Swedish population.

In general, the problems of using twin registries to study the etiology of cardiovascular disease with mortality and morbidity ratios in the neighborhood of 2 to 1 are much more difficult than in studying the etiology of bronchopulmonary disease in which the relationships are of the order of magnitude of 4 to 1.

8) TIEBLIN, G. Kommentar till en svensk tvillingundersökning. (Comment on research on twins in Sweden.) Lakartidningen 65 (47): 4654–4655, November 20, 1968.

(*157*) ROSE, G. A. The diagnosis of ischaemic heart pain and intermittent claudication in field surveys. Bulletin of the World Health Organization 27(6): 645–658, 1962.

(*158*) ROSE, G. A. Chest pain questionnaire. Milbank Memorial Fund Quarterly 43(2, part 2): 32–39, April 1965.

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Source: https://www.industrydocuments.ucsf.edu/docs/rrlk0000

Twin Registry. The criticisms of the Twin Registry noted here should also be compared with a subsequent letter by Burch (Lancet 1: 1283, 1972) and Letters to the Editor from Cherry and Forbes (Lancet 14 October, 1972) and Friberg (Lancet 4 November 1972). These are reproduced below.

SMOKING AND HEALTH

SIR,—Are we to judge from their silence that Dr. [illegible]'s critics have conceded his case (Jan. 29, p. 243, and [illegible] 11, p. 586)? Is cigarette-smoking non-lethal?

[illegible]he undoubted positive associations between cigarette [illegible]ing and death-rates from various diseases are not [illegible]al in origin, an alternative explanation is needed. [illegible]rding to Fisher,[1] such associations might arise from [illegible]nstitutional factors. That is to say, one or more of the [illegible]s that predispose to certain forms of smoking might be [illegible]ame as, or linked with, genes that predispose to fatal [illegible]ders such as lung cancer. In principle, we can dis-[illegible]inate between causal and constitutional hypotheses by [illegible]mining deaths in series of twins discordant for smoking [illegible]. The straightforward causal hypothesis predicts [illegible] deaths will occur earlier, on the average, in the smoking [illegible]bers of both monozygotic and dizygotic twin pairs. [illegible] constitutional hypothesis predicts that "early deaths" [illegible]ccur with equal frequency, on the average, among the [illegible]ing and the non-smoking members of monozygotic [illegible] pairs: where dizygotic twins are concerned, smokers [illegible]ld suffer an excess frequency of "early deaths" over [illegible] smokers.

[illegible]is simple test of the two hypotheses is, of course, [illegible]ered by the rarity of monozygotic twins discordant [illegible] smoking habits: only some 20–25% have been found [illegible]e strikingly discordant.[1,2]

[illegible]spite this obstacle, Friberg et al.[3] have obtained some [illegible]ging results. They studied deaths among 246 male [illegible]126 female monozygotic twin pairs, and in 706 male [illegible]781 female dizygotic twin pairs appreciably discordant [illegible]on-smoker" versus "smoker"; "less exposed" [illegible]s "more exposed"), and born in Sweden between [illegible] and 1925. Among the dizygotic male twins, deaths [illegible] recorded over a standard period as follows: 13 of [illegible] "non-exposed and less-exposed" as compared with [illegible] the "smoker and more exposed". Among dizygotic [illegible]le pairs, deaths were recorded in 18 of the "non-[illegible]osed and less-exposed" and 20 of the "smoker and [illegible]e exposed". Results for discordant monozygotic twins [illegible] very interesting: 14 deaths were recorded among [illegible] "non-exposed and less-exposed" men, but only 9 [illegible]ng the "smokers and more exposed"; among the [illegible]en, 4 of the "non-exposed and less-exposed" and 6 of [illegible] "smoker and more exposed" died. Overall, the "more [illegible]osed" (sexes combined) enjoyed a slight but not signifi-[illegible] advantage (18/15) over the "non-exposed and less-[illegible]osed". On a formal statistical test, the difference in mor-[illegible]ity ratios ("non-exposed and less-exposed"/"smoker [illegible] more exposed") between the sets of monozygotic and [illegible]gotic male twins corroborates the constitutional hypo-[illegible]s and rejects (at the 1–2% level) the causal hypothesis [illegible]with Yates' correction = 5·78; $0{\cdot}01 < P < 0{\cdot}02$). How-[illegible], this result needs to be treated with caution because [illegible] degree of discordance for smoking habits between the [illegible]ozygotic and dizygotic series, although similar, was [illegible]ably not identical. This reservation apart, the indepen-[illegible] findings of Friberg et al.[3] support Dr. Seltzer.

[illegible]rhaps the issue could be put beyond reasonable doubt [illegible]supplementing the study of Friberg and his colleagues [illegible] a world-wide survey under the ægis, say, of the World Health Organisation? And why should not the cigarette manufacturers foot the bill?

[illegible] General Infirmary, P. R. J. BURCH.

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SMOKING AND HEALTH

SIR,—Professor Burch [1,2] calls for a worldwide twin study to distinguish between causal and constitutional factors in the association between cigarette smoking and disorders such as coronary heart-disease and lung cancer. This proposal is based on the results obtained by Friberg et al.[3] for monozygotic and dizygotic twins which suggest to Friberg and Burch that differences in mortality between populations of smokers and non-smokers are a consequence of differences in genetic and other inherited factors.

This interpretation of Friberg's results is open to several criticisms. First, the published data provide no direct information about differences in mortality within individual *pairs* of twins. That is, the data only provide information about deaths in two populations, each member of which happens to have a twin in the other population; it is not stated in how many instances both, one, or no twins in a pair have died. Hence, data permitting comparisons within twin pairs, where one twin serves as a control for the other (which represents the unique value of this type of experiment), are not available to the reader. For example, for monozygotic twins, where Friberg observes approximately equal numbers of deaths for non-smokers and smokers—viz., 4 vs 5, and 4 vs 6 deaths, respectively; for males and females, it is possible that, on average, the smokers died at an early age.

Secondly, it must be noted that some of the reported data only represent approximations, since two groups of smokers have overlap; a "less exposed" group, which is considered with non-smokers, includes smokers of up to 20 cigarettes per day, whereas a "more exposed" group, which is considered with smokers, includes smokers of down to 10 cigarettes per day. Such an approach does not provide a clear distinction between categories of amounts smoked. Also, the intra-pair differences to smoking exposure might be less for the monozygotic than for the dizygotic pairs, because of constitutional factors which might influence smoking discordancy.

For these and other reasons, it is appropriate to re-examine the methods of presentation and analysis. A discussion along these lines has been presented previously.[4] Be-

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cause linking cigarette smoking causally to various diseases has, for some time, been sufficiently strong to concentrate efforts on reducing or eliminating the hazards of cigarette smoking.[5–8] This conclusion does not deny the fact that there remain numerous questions concerning the action of cigarette smoking, which remain to be solved. One of these is the role of genetic factors which may contribute to a person taking up various forms of smoking or contracting individual diseases. A worldwide twin study, as suggested by Professor Burch, would take a number of years to complete; and since, at present, there is little evidence that such a study would alter the main conclusions concerning the effects of cigarette smoking on health, a lower priority should be given to such a study than to research on reducing the accepted hazards.

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W. H. CHERRY
W. F. FORBES.

SMOKING AND HEALTH

SIR,—In the comments of Dr. Cherry and Professor Forbes (Oct. 14, p. 824) on the proposal of Professor Burch [1,2] to embark on worldwide twin studies, our report from the Swedish registry on mortality in smoking discordant monozygotic and dizygotic twins [3] is criticised to some extent.

Dr. Cherry and Professor Forbes point out that the data provide no information on what has happened within the individual *pairs* of twins, since it was not stated in how many instances both, one, or no twins in a pair had died. We agree that such analysis is of importance where a substantial number of concordant deaths occur. Concerning the crucial group (male twin pairs born 1901–25), where differences between dizygotic and monozygotic twins were found, however, only one pair in the dizygotic group (non-smoker/smoker in age-group 1901–10) and one pair in the monozygotic group ("less exposed"/"more exposed" in age-group 1901–10) showed concordant death. Thus the findings reported actually refer to differences within individual *pairs* of twins. For our future reports, when a larger number of concordant deaths can be expected, no doubt one should also take the year of death into consideration. At the time of our report [3] such an analysis would not have been meaningful.

We appreciate the comments, but when Dr. Cherry and Professor Forbes mean that what they point out may invalidate our interpretation of the data presented, we must disagree. Also, we are surprised about their comments, because already, in a personal letter, Professor Forbes received a complete set of data showing the number of twins in the mentioned age-groups, divided into dizygotic and monozygotic pairs, from which it was easily seen in how many instances both, one, or no twins in a pair had died.

Dr. Cherry and Professor Forbes are sceptical of Professor Burch's proposal of worldwide twin studies. One reason given is that, at present, there is little evidence that such studies would alter the main conclusions concerning the effects of cigarette smoking on health. For certain pulmonary diseases (e.g., lung cancer) the causal relationship with cigarette smoking is quite clear. On the other hand, twin studies might well be of substantial value even for these effects—for example, to find out whether certain persons are more susceptible than others to an effect of cigarette smoking. For other effects, including high mortality in general and particularly, for example, in coronary heart-disease, we feel that the case against cigarette smoking per se is not all that strong and in our opinion international collaboration using twins as target populations would be extremely useful. The problem in twin studies, even using a population the size of Sweden's, is to get enough numbers in different, well-defined smoking discordant groups. We are happy to learn that Dr. Cherry and Professor Forbes do not live up to their own objections to creating new registries. As can be seen in a recent paper of theirs,[9] they state, "A twin study is being planned, partly to investigate further the observations, on smoking discordant twins, reported by Friberg et al."

Finally, we wish to point out that international collaboration on twin studies should not be carried out with the sole aim of studying effects of tobacco on health. Certainly, as was pointed out at an international symposium on twin registries in the study of chronic disease,[6] in advocating the establishment of new large-scale twin registries, it should be recognised that such registries constitute valuable national resources for investigations into the causes and prevention of disease. While large-scale twin studies until now have primarily focused on the health consequences of smoking, the twin method has a much broader applicability to a large number of medical and social problems concerned with the interrelationships between environmental agents and their impact upon the genetic constitution. The importance of these interrelationships was precisely the reason for a recent expansion of the Swedish twin registry in collaboration with the National Environment Protection Board to include an additional 15,000 pairs born from 1926 to 1942.

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LARS FRIBERG.

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More recently, Friberg, et al. (*69*) reported on mortality data from the Swedish Twin Registry. The authors suggested that part of the increased mortality observed among smokers when compared with nonsmokers was not due to smoking per se but to factors associated with smoking. The very small numbers of total deaths presently available (47 deaths among 706 dizygotic pairs and 13 deaths among 246 monozygotic pairs) do not provide a statistically stable base for deriving any conclusions at the present time.

(*69*) Friberg, L., Cederlof, R., Lundman, T., Olsson, H. Mortality, smoking discordant monozygotic and dizygotic twins. A study on the Swedish Twin Registry. Archives of Environmental Health 21(4): 508–513, October 1970.

Hauge, et al. (*81*) have recently reported on the influence of smoking on the morbidity and mortality observed in the Danish Twin Register. Among 762 monozygotic and same-sexed dizygotic twin pairs, angina pectoris was found to be significantly more frequent in those cotwins with a higher consumption of tobacco than in those with a lower or no consumption. A similar tendency was observed for myocardial infarctions but was not of statistical significance.

(*81*) Hauge, M., Harvald, B., Reid, D. D. A twin study of the influence of smoking on morbidity and mortality. Acta Geneticae Medicae et Gemellologiae 19: 335–336, 1970.

Seltzer, who has been a proponent of the constitutional hypothesis, in a recent review of some of the experimental, clinical, and pathological data relating smoking and CHD, concluded that the evidence from these areas has not "reasonably substantiated" the "hypothesis" of the acute effect of cigarette smoking on the coronary circulation, nor has the chronic effect of cigarette smoking on the cardiovascular system been shown to be a "clear" and consistent one (*170*). His views are contrary to those of most researchers in this field.

(*170*) Seltzer, C. C. The effect of cigarette smoking on coronary heart disease. Where do we stand now? Archives of Environmental Health 20(3): 418–423, March 1970.

Although the data from the twin studies are inconclusive with regard to a role for genetic factors in heart disease, it would be surprising if genetic factors did not play such a role. It is open to question whether findings from twin studies can be used to distinguish between the hypothesis that genetic factors govern the level of host susceptibility or resistance to the effects of an exogenous influence such as cigarette smoking and the hypothesis that genetic factors "cause" both heart disease and smoking.

EXPERIMENTAL STUDIES CONCERNING THE RELATIONSHIP OF CORONARY HEART DISEASE AND SMOKING

Several areas of interest in cardiovascular pathophysiology have been investigated in the search for the mechanisms by which cigarette smoking contributes to cardiovascular disease, particularly coronary artery disease. Previous Public Health Service Reviews (*191*, *192*, *193*, *198*) have described in detail and commented on the results of experiments by many teams of researchers.

(*191*) U.S. Public Health Service. The Health Consequences of Smoking. A Public Health Service Review: 1967. Washington, U.S. Department of Health, Education, and Welfare, Public Health Service Publication No. 1696, 1967. 199 pp.

(*193*) U.S. Public Health Service. The Health Consequences of Smoking. 1969 Supplement to the 1967 Public Health Service Review. Washington, U.S. Department of Health, Education, and Welfare, Public Health Service Publication No. 1696-2, 1969. 98 pp.

(*198*) U.S. Public Health Service. Smoking and Health. Report of the Advisory Committee to the Surgeon General of the Public Health Service. Washington, U.S. Department of Health, Education, and Welfare, Public Health Service Publication No. 1103, 1964. 387 pp.

Central to the discussion which follows is a concept of cardiac physiology which provides a framework for analysis and understanding of the varied research. That concept concerns the dynamic balance between myocardial oxygen need and supply.

Cardiovascular Effects of Cigarette Smoke and Nicotine

The inhalation of tobacco smoke or the parenteral administration of nicotine has been found by many researchers to be associated with a number of specific acute cardiovascular responses. These responses have been observed in human as well as animal subjects, including increased heart rate, blood pressure, cardiac output, stroke volume, velocity of contraction, myocardial contractile force, myocardial oxygen consumption, arrhythmia formation, and electrocardiographic or ballistocardiographic changes (tables A 20 to A 22). The effect of these responses on coronary blood flow will be discussed in a following section.

That the acute effects observed following the inhalation of cigarette smoke are due primarily to the nicotine present in the smoke may be seen in the results of a number of experiments. In humans, Irving and Yamamota (*89*) and Von Ahn (*202*) duplicated the effects of cigarette smoking by the administration of nicotine intravenously. Similar results in animals were noted by Kien and Sherrod (*112*).

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(*89*) Irving, D. W., Yamamoto, T. Cigarette smoke and cardiac output. British Heart Journal 25: 126–132, 1963.

(*202*) Von Ahn, B. Tobacco smoking, the electrocardiogram, and angina pectoris. Annals of the New York Academy of Sciences 90(1): 190–198, September 27, 1960.

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Constitutional Hypothesis. The document has answered (170) Seltzer by stating that his views are contrary to those of most researchers in this field. The article is reproduced in its entirety.

The Effect of Cigarette Smoking on Coronary Heart Disease

Where Do We Stand Now?

Carl C. Seltzer, PhD, Boston

IT IS AN ESTABLISHED observation that there is a statistically significant association of cigarette smokers and increased mortality and morbidity from coronary heart disease (CHD) in men. It forms the basic springboard for public health warnings as to the health hazards of cigarette smoking and CHD. But it does not tell us how smoking causes or precipitates a death from CHD, or if indeed it does. The most such an observation can do is to demonstrate the existence of a relationship; it cannot establish any existing relationship as a causal one. For this, it is necessary to derive biological inferences from other evidence, pathological, clinical, experimental, as well as epidemiological. What follows is an analysis as to where we are now with respect to the biological inferences, and not necessarily where we will be in the future, since all the facts are not yet in and many of the conclusions and concepts will need more documentation.

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A convenient starting point is the *Surgeon General's Advisory Committee's Report* of 1964. After considering all the available information on smoking and CHD, the committee concluded that "male cigarette smokers have a higher death rate from coronary artery disease than non-smoking males, but it is not clear that the association has causal significance."[1] However, since 1964 there has accumulated a considerable body of data bearing on this area of concern, and it is from this additional evidence that we can best judge where we now stand on the effect of smoking on CHD. Epidemiological, pathological, experimental, and clinical evidence will be examined in turn.

Epidemiological Evidence

Recently, I reviewed the new epidemiological evidence.[2] The conclusion of the Surgeon General's 1964 report that male cigarette smokers have a higher death rate from CHD than men who do not smoke has been confirmed in the new studies published since the report was issued. Prospective studies of smoking and death rate gave a median mortality ratio (current cigarette smokers to nonsmokers) of 1.7, with no appreciable excess in deaths among cigar and pipe smokers. Angina pectoris, which represents about 20% of all manifestations of CHD, was fo

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the most part found to be unrelated to cigarette smoking. Significantly, duration of cigarette smoking was found to be unassociated with excess CHD mortality, and conflicting results were obtained with regard to the effect of cigarette smoke inhalation. There also were a number of inconsistencies and inversions in reports of a consistent, rising gradient of CHD mortality with increasing amounts of cigarettes smoked. Those who smoked the most cigarettes had higher CHD rates than those who smoked the least, but the disease rates of the those smoking intermediate amounts were almost invariably the same or lower than those of those who smoked the least. The data dealing with discontinuance of smoking gave contractory and inconsistent findings and reflected on the problem of drawing valid conclusions from such data in exsmokers. In sum, collateral epidemiological evidence related to reasonable mechanisms was found to be weak, negative, or nonsupportive.

This in no way obviates the basic observation that cigarette smokers show excess mortality and disability from CHD, including sudden death. This observation still stands and commands attention and explanation. It means that the collateral epidemiological evidence is not supportive with respect to CHD as similar evidence is for smoking and other diseases, such as lung cancer and chronic bronchitis.

Pathological Evidence

It has been hypothesized that cigarette smoking has a long-term effect on CHD through a cumulative process of augmentation of atherogenesis.[3] The studies of Auerback et al[4] and Strong et al[5] in hospital autopsy cases found advanced degrees of atherosclerosis to be higher among cigarette smokers than among nonsmokers and increased with amount of smoking.

In more recent studies of populations likely to be less selected for arterial disease or smoking habit, Viel and associates[6] found "no relationship between atherosclerotic lesions and the use of tobacco" in an autopsy study of violent deaths (ages 10 to 70 years). In another study of violent deaths among consecutive accident victims (ages 16 to 49 years) Benson and Galindo (written communication, Jan 1968) found no significant differences in amount and type of atherosclerosis between smokers and nonsmokers. As noted by W. Kannel, MD (oral communication, August 1969), the autopsy series of the Framingham Study shows no correlation of degree of uncomplicated coronary artery atherosclerosis and the antecedent premorbid cigarette smoking habit.

That cigarette smoking has a chronic or cumulative effect leading to advanced degrees of atherogenesis is, also, inconsistent with several established observations: that duration of cigarette smoking is not associated with excess deaths from CHD,[7-9] with the lack of uniform evidence of an association of cigarette smoking with angina pectoris, and with the decreased statistical association of cigarette smoking and CHD in older subjects. The evidence, then, for a long-term effect of cigarette smoking contributing to excess CHD through a process of augmentation of atherosclerosis is not clear-cut, and is inconsistent with other pertinent information.

Clinical and Experimental Evidence

This section deals with the acute effects of cigarette smoking. These effects rather than the possible long-term effects of smoking are the present major basis of suspicion of harm to the cardiovascular system.[10] Of the various components of tobacco smoke with acute pharmacologic effects, the focus until recently was almost exclusively on nicotine. Lately, other constituents of tobacco smoke, principally carbon monoxide, have also been receiving attention.

Much is known concerning the acute cardiovascular effects of nicotine in man and experimental animals. In low concentrations, nicotine stimulates the sympathetic and parasympathetic ganglia, and in high concentrations, paralyses them. Thus, nicotine can cause liberation of catecholamines from the adrenal medulla. Nicotine can also have a sympathomimetic effect by causing the discharge of epinephrine and norepinephrine from chromaffin cells in various tissues, and in addition, can produce effects reflexly by stimulating the chemoreceptors of the carotid and aortic bodies. The net results are transient, noncumulative, reversi-

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ble increases in heart rate; cardiac output, ie, cardiac work; systolic blood pressure; and in rate and depth of breathing.

The Surgeon General's 1964 committee reviewed and analyzed the large body of data available to them on the acute effects of cigarette smoking and found "no unique cardiovascular effects" were demonstrated to "seem likely to account for the observed association of cigarette smoking with an increased incidence of coronary disease."[1] The conclusions were based on the effects of nicotine; carbon monoxide was not considered.

Since then there has accumulated a considerable amount of additional experimental material. These data have led the Public Health Service to advance the theoretical concept of mechanisms, whereby ". . . in the presence of impaired coronary circulation due to coronary heart disease, cigarette smoking may 'trigger' myocardial oxygen deficits of critical degree" leading to myocardial infarction and sudden death.[10]

Let us examine the more important of these mechanisms. This can be done best by posing a number of questions and attempting to answer them on the basis of the present evidence.

1. Does cigarette smoking "trigger" or "contribute to" increased incidence of acute myocardial infarction or sudden death through critical reductions in coronary nutrient capillary blood flow? The evidence that it could rests on the observations that cigarette smoking creates increased myocardial oxygen demands owing to the nicotine-induced catecholamine effect, and that while in normal persons the response is a compensatory increase in coronary blood flow, in some CHD patients, the compensatory increase in blood flow is absent.[11] The problem then rests on how critical is the absence of compensatory increase in coronary blood flow in persons with already impaired coronary circulation, in the light of differences in amount and frequency of smoking, of the condition and activity level of the patient, and considering that the effects of smoking are transient and noncumulative. The evidence on these points is not yet available; the question is challenging and remains to be answered.

2. Does cigarette smoking "trigger" myocardial oxygen deficit of a critical degree through "the impairment of coronary blood as a result of the increased blood viscosity associated with hyperlipemia and hemoconcentration"[10] It has been reported that hemoconcentration occurs both in cigarette smokers and in patients with myocardial infarction, and that increased fatty acids increase the force necessary to "shear" blood. However, conflicting results have been obtained with respect to hemoconcentration in persons with CHD.[12,13] The concepts of viscosity of blood as influenced by rate of shear and hematocrit value are presently, as Burch and DePasquale[14] point out, "highly speculative." The whole question is exceedingly complex. There are no data directly relating smoking to fatal CHD events through measurable increased blood viscosity in patients with CHD. This interesting concept is still hypothetical and without documentation.

3. Does cigarette smoking, by a catecholamine effect, "trigger" myocardial oxygen deficit of a critical degree through "the increase of myocardial wall tension and velocity of contraction?"[10] That nicotine or cigarette smoking or both, augment heart muscle contractility and consequently increase myocardial oxygen need, is consistent with the evidence. The extent of the increase in oxygen demand, however, is imperfectly known and dependent on factors involved in the complexity of myocardial energetics and nicotine absorption. Where, when, in what circumstances are the levels of oxygen requirements occasioned by increased myocardial contractility not met? The answer to the question is still to come.

4. Does cigarette smoking "trigger" myocardial oxygen deficit of a critical degree "through a predisposition to acute arrhythmias as a consequence of harmful neurogenic reflexes or catecholamine release?"[10] Support for this hypothesis comes, in part, from experimental studies in dogs in which direct administration of nicotine induced varying effects on the complicated neural and humoral mechanisms affect heart rate and rhythm, and an enhancement of Purkinj fiber "automaticity."[15,16] Webb et al showed, following bipolar ventricular electrode stimulation of dogs, a postresponse to cigarette smoking in which hemodynamic

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changes quickly returned to normal, and the fibrillation threshold declined slowly and eventually fell below threshold baseline. As far as studies in humans are concerned, there appear to be no hard facts on this subject, no conclusive evidence that cigarette smoking precipitates "serious, life-threatening arrhythmias." But since arrhythmias can lead to clinical disability and death it is important that this subject be thoroughly investigated.

5. Does cigarette smoking lead to thrombus formation? In the presence of impaired coronary artery circulation, does cigarette smoking "trigger" myocardial oxygen deficit of a critical degree through an increase in platelet adhesiveness?

Helpful reviews of the literature on smoking and thrombosis have been provided by Murphy and Mustard[18,19] and again most recently by Murphy.[20] These authors find no satisfactory answer to the question, "Does smoking lead to thrombus formation?" They note that the experimental approach with laboratory animals is replete with difficulties in simulating human cigarette smoking, and that the assessment of thrombosis is a problem since the techniques used do not represent thrombosis but clotting of shed blood. The problem of microthrombi is even more difficult.

Murphy and Mustard note that actual experimental work in connection with smoking and thrombus formation is scanty, and consider inconclusive the results of Engelberg and Futterman,[22] who used the Chandler loop, in which a significant reduction in thrombus formation time was reported in some subjects after they smoked two cigarettes. In answer to the question, "Which constituents in tobacco smoke are producing the effect?" Murphy and Mustard state that there is "embarrasingly little information" and no formal conclusions can be drawn. They note that the evidence at present is circumstantial while they indicate that "nicotine may be responsible." After consideration of the studies relating the platelet, arterial wall, coagulation, and fibrinolysis to thrombogenesis, the reviewers conclude:

> The evidence, so far, suggests the tentative conclusion that smoking is associated with a transient increase in tendency to form thrombi and this result could be largely explained by the release of endogeneous epinephrine by absorbed nicotine.

Studies of Spain et al[21] and Engelberg and Futterman[22] do ntt support the suggestion that cigarette smoking may precipitate acute coronary artery events by altering the blood coagulability as a result of stimulation to catecholamine production and free fatty acid mobilization.

Because of the difficulty of studying thrombus formation in man, special emphasis has been placed on blood coagulation, even though coagulation and thrombus formation are not identical. In studying possible smoking effects on thrombus formation in man, observers have relied heavily on in vitro phenomena with the attendant problems of experimental control and of transposing in vitro results to intact man. It is possible that clotting may be the least important mechanism in the thrombotic development, and that thrombosis will only occur when vessel damage is present and when there is decreased flow through vasoconstriction.

At the present state of our knowledge, it is possible that release of endogeneous epinephrine through nicotine absorption may produce transient increases in platelet aggregation in some persons. But this evidence is confounded with factors inherent in the nature of the experiments and in man's great variation and unique homeostatic propensities. Even if experimental methods and design were adequate, the question of smoking and thrombus formation would still remain an extremely difficult problem. From the evidence now available, no firm conclusion is possible that cigarette smoking so affects the thrombus forming process in human blood as to account for a portion of the excess deaths from CHD that occur in cigarette smokers.

6. Does the carbon monoxide constituent of cigarette smoke result in or contribute to increased myocardial infarction or sudden death either in normal individuals or in persons with already impaired coronary circulation due to CHD?

Studies have shown that the carbon monoxide constituent of cigarette smoke does effect increases (2% to 10%) in the levels of carboxyhemoglobin (COHb) saturation when heavy cigarette smokers and nonsmok-

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ers were compared, with the consequent displacement of oxyhemoglobin. In addition, carbon monoxide effects a shift to the left of the oxygen-hemoglobin dissociation curve, which may result in a decreased release of oxygen at the tissue level.[23]

On the whole, experimental and clinical investigations bearing on this question are few. The most salient work in this area has been performed by Ayres and associates.[24] In 26 human subjects before and after carbon monoxide inhalation, these investigators found no significant change in oxygen tension. In another experiment, after exposure to carbon monoxide, coronary blood flow increased significantly in seven non-CHD patients but not in four patients with arteriographically proven CHD. In the patients with CHD, myocardial lactate and pyruvate extraction decreased or shifted to actual production, suggesting anaerobic metabolism.

If carbon monoxide does in fact appreciably decrease oxygen extraction at the myocardial level, the matter of oxygen consumption may hinge on the extent of increase in coronary blood flow in normal persons, while in persons with diseased coronary arteries, the increase in blood flow is slight or absent. Hence, it may be a question of the ultimate balance of these opposing forces. In normal persons, there is the presumption that the increased coronary blood flow more than matches the presumed decrease in oxygen extraction. Whether or not this fails to occur in patients with obvious CHD, to such an extent as to "trigger" a coronary event is as yet unknown and much work remains to be done in this area.

Summary

Where do we now stand? Certain facts are clear. It is clear that there is a higher mortality rate from cardiovascular disease in cigarette smokers than in nonsmokers. The epidemiological evidence about duration of smoking, inhalation, amount of smoking, and stopping smoking has been shown to be inconclusive or less supportive with respect to CHD than for smoking and other diseases. A chronic effect of cigarette smoking is not clear and is inconsistent with other information. As far as acute effects are concerned, a series of physiological mechanisms have been advanced whereby cigarette smoking could trigger myocardial oxygen deficits of a critical degree in the presence of impaired coronary circulation due to CHD. This hypothesis has not been reasonably substantiated. Some of the evidence is provocative, but in many instances the hypothesized mechanisms are inadequately documented or not documented at all.

The statistical association of higher mortality from CHD in cigarette smokers still remains to be explained. An explanation may lie in a constitutional and genetic predisposition both to cigarette smoking and CHD. A genetic factor in the etiology of CHD is well accepted, and there is a growing body of evidence that smokers are different from nonsmokers in a large variety of biological ways and behavioral patterns, including "style of life."[25,26] If smokers show a greater tendency toward heart disease than nonsmokers because they are different kinds of people than nonsmokers—more vulnerable constitutional types—this could explain the comparatively low degree of association (mortality ratio of 1.7) of excess heart disease among cigarette smokers. At present, this has not been fully established. More research in this area is vitally necessary.

The *Surgeon General's Advisory Committee's Report* on "Smoking and Health" concluded in 1964 that "male cigarette smokers have a higher death rate from coronary heart disease than nonsmoking males, but it is not clear that the association has causal significance."[1] I believe this is where we still stand.

We are mindful that absolute proof is unattainable. We are also mindful, however, of the hazards of inadequate knowledge. More work must be done and new information gathered until the crucial questions are illuminated.

Assuredly, this opinion cannot be satisfying to those readers who are seeking a yes and no answer to the question whether or not cigarette smoking carries a serious risk of CHD. Fair-minded persons will concede that this opinion is mainly due to the unsatisfactory state of the evidence, which only time and more intensive study will resolve.

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14. Burch, G.E., and DePasquale, N.P.: The Hematocrit in Patients With Myocardial Infarction, *JAMA* 180:63-65 (April 7) 1962.

15. Nadeau, R.A., and James, T.N.: Effects of Nicotine on Heart Rate Studies by Direct Perfusion of Sinus Node, *Amer J Physiol* 212:911-916 (April) 1967.

16. Greenspan, K.; Knoebel, S.B.; and Fisch, C.: Effect of Nicotine Upon Human and Canine Cardiac Action Potential and Contractile State, abstracted, *Project for Research on Tobacco and Health 1964-1968: Report to the Profession and Abstracts of Grants*, Chicago, AMA-ERF, June 1968, p 24.

17. Webb, W.R.; Wax, S.D.; and Sugg, W.L.: Cigarette Smoke and Fibrillation Threshold in Dogs, abstracted, *Clin Res* 16:74 (Jan) 1968.

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The mechanism by which cigarette smoke and hence nicotine induces these changes has been of interest to numerous investigators. Nicotine has long been known as a stimulator of both sympathetic and parasympathetic ganglia. Research has centered, therefore, on the function of catecholamines, mainly epinephrine and norepinephrine, as mediators, of these responses. Using isolated rabbit atrial myocardium, Burn and Rand (*35*) noted that the prior administration of reserpine to the perfusate blocked the increased rate and amplitude of contraction seen following the administration of nicotine. West, et al. (*208*) showed that the *in vivo* cardiac stimulating effect of nicotine was blocked by tetraethylammonium chloride. Leaders and Long (*125*), Romero and Talesnik (*156*), and, more recently, Ross and Blesa (*160*) have all demonstrated this blockade in animals using agents such as pentolinium, hexamethonium, guanethidine, and reserpine.

More direct evidence of the catecholamine-releasing effect of nicotine has been found by Watts (*202*) and Westfall, et al. (*209, 210, 211*) (table A22). Among animal subjects, nicotine administration and the inhalation of the smoke of standard cigarettes caused significant increases in peripheral arterial epinephrine levels, while cornsilk cigarette smoke inhalation evoked no such change. In humans, cigarette smoking was found to be associated with a significant increase in urinary epinephrine excretion.

The source of these nicotine-released catecholamines, particularly those which mediate the immediate and local cardiac responses to intracoronary injections of nicotine, is felt to be the myocardial chromaffin tissue (*35, 160*). The more widespread effects are most probably mediated by hormones released from the adrenal gland.

According to recent research of Saphir and Rapaport, catecholamine release may not be the sole mediator of these responses (*166*). These investigators reported that intra-arterial injections of nicotine into the mesenteric circulation of cats were followed within 1 to 2 seconds by enhanced myocardial performance, increased left ventricular systolic pressure, and increased systemic resistance. Sectioning of the mesenteric afferent nerves led to a diminished response. The authors concluded that the cardiovascular response to nicotine may also be neurogenic in nature. Nadeau and James (*142*) injected nicotine directly into the sinus node artery of dogs and noted an initial bradycardia, due probably to direct vagal stimulation, followed by tachycardia, due probably to catecholamine release.

That the presence of nicotine may predispose the myocardium, particularly a hypoxic or previously damaged myocardium, to arrhythmia formation is suggested by the research of Balazs, et al. (*16*), Bellet, et al. (*21*), and Greenspan, et al. (*74*). Balazs produced myocardial lesions in dogs either by pretreatment with isoproterenol or ligation of the anterior descending coronary artery. It was found that while normal animals did not develop arrhythmias upon challenge with small doses of intravenous nicotine, some animals with damaged myocardiums responded with increased arrhythmia formation shortly after their spontaneous arrhythmias had ceased. More recently, Bellet, et al. (*20*) studied the effect of cigarette smoke inhalation on the ventricular fibrillation threshold in anesthetized dogs. They observed a statistically significant decrease in the threshold following smoke inhalation. Greenspan, et al. (*74*), using isolated dog right ventricular myocardium, observed that nicotine perfusion increased the automaticity of the Purkinje fibers system and decreased the conduction velocity. The authors consider that these two nicotine-induced effects probably predispose the myocardium to the initiation of arrhythmias.

(*118*) KIEN, G. A., SHERROD, T. R. Action of nicotine and smoking on coronary circulation and myocardial oxygen utilization. Annals of the New York Academy of Sciences 90(1): 161–173, September 27, 1960.

(*35*) BURN, J. H., RAND, M. J. Action of nicotine on the heart. British Medical Journal 1: 137–139, January 18, 1958.

(*208*) WEST, J. W., GUZMAN, S. V., BELLET, S. Cardiac effects of intracoronary arterial injections of nicotine. Circulation Research 6: 389–395, May 1958.

(*125*) LEADERS, F. E., LONG, J. P. Action of nicotine on coronary vascular resistance in dogs. American Journal of Physiology 203(4): 621–625, October 1962.

(*156*) ROMERO, T., TALESNIK, J. Influence of nicotine on the coronary circulation of the isolated heart of the cat. Journal of Pharmacy and Pharmacology 19(5): 322–323, 1967.

(*160*) ROSS, G., BLESA, M. I. The effect of nicotine on the coronary circulation of dogs. American Heart Journal 79(1): 96–102, January 1970.

(*202*) WATTS, D. T. The effect of nicotine and smoking on the secretion of epinephrine. Annals of the New York Academy of Sciences 90(1): 74–80, September 27, 1960.

(*209*) WESTFALL, T. C., CIPOLLONI, P. B., EDMUNDOWICZ, A. C. Influence of propranolol on hemodynamic changes and plasma catecholamine levels following cigarette smoking and nicotine. Proceedings of the Society for Experimental Biology and Medicine 123: 174–179, 1966.

(*210*) WESTFALL, T. C., WATTS, D. T. Effect of cigarette smoke on epinephrine secretion in the dog. Proceedings of the Society for Experimental Biology and Medicine 112(4): 843–847, April 1963.

(*211*) WESTFALL, T. C., WATTS, D. T. Catecholamine excretion in smokers and nonsmokers. Journal of Applied Physiology 19(1): 40–42, January 1964.

(*166*) SAPHIR, R., RAPAPORT, E. Cardiovascular responses of the cat to mesenteric intra-arterial administration of nicotine, cyanide and venous blood. Circulation Research 25(6): 713–724, December 1969.

(*142*) NADEAU, R. A., JAMES, T. N. Effects of nicotine on heart rate studied by direct perfusion of sinus node. American Journal of Physiology 212(4): 911–916, April 1967.

(*16*) BALAZS, T., OHTAKE, S., CUMMINGS, J. R., NOBLE, J. F. Ventricular extrasystoles induced by epinephrine, nicotine, ethanol, and vasopressin in dogs with myocardial lesions. Toxicology and Applied Pharmacology 15(1): 189–205, July 1969.

(*21*) BELLET, S., KERSHBAUM, A., MEADE, R. H., JR., SCHWARTZ, L. The effect of tobacco smoke and nicotine on the normal heart and in the presence of myocardial damage produced by coronary ligation. American Journal of the Medical Sciences 201(1): 40–51, January 1941.

(*74*) GREENSPAN, K., EDMANDS, R. E., KNOEBEL, S. B., FISCH, C. Some effects of nicotine on cardiac automaticity, conduction, and inotropy. Archives of Internal Medicine 123(6): 707–712, June 1969.

(*20*) BELLET, S., FISCHMANN, D., ROMAN, L., DEGUZMAN, N. The effect of cigarette smoke inhalation on the ventricular fibrillation threshold. Circulation (Supplement 3) 42(4): 135, October 1970.

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Source of Catecholamines. Since (35) Burns and Rand and (160) Rose and Blasa used either the isolated heart or the intact heart with intracoronary injection of nicotine, the source of catecholamines will have to be from the heart. However, with inhalation of cigarette smoke, the more important source is adrenal gland which was demonstrated by (210) Westfall and Watts. Portions of this article are reproduced below.

The site of release is an important point for the thesis appearing in the document. A cardiac source would mean high level of catecholamines whereas an adrenal source would mean low level of amines reaching the heart.

Discussion. These results show that inhalation of cigarette smoke can cause a significant increase in secretion of epinephrine from the adrenal gland of the dog. It is well established that nicotine is the chief pharmacologically active substance in cigarette smoke (16,17). Nicotine in large doses can cause the release of catecholamines from the adrenal gland(2,3,4). Control experiments involving no smoking and the smoking of cornsilk cigarettes had no effect on epinephrine secretion. The effect of asphyxia and hypoxia was very small when compared to cigarette smoking. The data indicate it is the nicotine in the smoke which produced the observed responses.

It is apparent that the increase in epinephrine content during smoking is greatest in the vena cava blood, followed by the arterial and peripheral venous blood, respectively. The vena cava blood contains the immediate secretions from the adrenal glands diluted by blood flow from the posterior part of the body only. By the time the secretions from the adrenal glands reach peripheral arterial blood, the epinephrine has been further diluted by the total venous return and possibly by inactivation in the lungs. Finally, epinephrine content is further decreased by passage through the tissues of the hind leg so the lowest concentration appears in the peripheral venous blood. Further significance is placed on the fact that inhalation of cigarette smoke produced an increase in epinephrine levels of peripheral arterial blood since this is the blood which reaches all tissues. To simulate more closely cigarette smoking in humans, experiments were carried out in which inhalation of cigarette smoke was controlled at a slow rate. Smoking time in these experiments was 8 minutes which is comparable to the average human cigarette smoking time. The results show that from control levels of less than 1 μg·l the slow inhalation of cigarette smoke increased epinephrine levels of peripheral arterial blood to 25.1 μg l ($p<0.001$). This elevation in epinephrine levels was found to increase progressively to a maximum value during the smoking period. In the previous experiments, where average smoking time was 3.5 minutes, inhalation of cigarette smoke caused an increase in arterial epinephrine level from an undetectable amount before the cigarette to a value of 126 μg l during the cigarette. Although consideration must be given to species and weight differences, these results indicate that a similar effect can occur in man during cigarette smoking.

Results obtained in this study on the differential release of epinephrine and norepinephrine are in agreement with results reported in the literature on release of epinephrine and norepinephrine by nicotine(10-14) in that the increase of catecholamines in the peripheral circulation is due primarily to a release of epinephrine from the adrenal medulla.

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AUTOPSY STUDIES RELATING SMOKING, ATHEROSCLEROSIS, AND SUDDEN CHD DEATH

A number of researchers have investigated the cigarette smoking habits and the cardiovascular pathology of those individuals dying suddenly from CHD and of large populations of individuals with and without histories of overt CHD.

Spain and Bradess (*175*) recently analyzed the smoking habits of 189 individuals who died suddenly and unexpectedly, apparently from the first acute clinical episodes of CHD. The authors noted a close correlation of a history of cigarette smoking with this type of sudden death and also with shorter survival times following the acute episode. This association was strongest in those persons under 50 years of age.

The authors also observed that those surviving very short periods of time showed a notable lack of intracoronary artery thrombi at autopsy and that the frequency of thrombi present increased with increasing survival time. They suggested that thrombi found at autopsy may be the result rather than the cause of certain instances of myocardial infarction, particularly of lesions showing subendocardial necrosis. This finding is of significance in the study of the effect of smoking on myocardial metabolism and oxygen supply and demand rather than on thrombus or platelet plug formation.

While the autopsy study of Spain and Bradess (*175*) concerned sudden death among smokers, other autopsy studies from various countries have been directed towards the relationship of cigarette smoking to the presence of atherosclerotic disease in the aorta and coronary arteries. These are concerned with the long-term effects which smoking has on the cardiovascular system and are summarized in table 19. The studies of Auerbach, et al. (*12*), Avtandilov, et al. (*13*), Sackett, et al. (*165*), and Strong, et al. (*182*) found that aortic and coronary atherosclerosis were more common and more severe among smokers than among nonsmokers. Auerbach, et al. (*12*) noted that this relationship persisted when the cases were matched for both age and cause of death or when the following cases were excluded: men with a history of diabetes; men who had died of any type of heart disease; and men whose hearts weighed 400 grams or more. Sackett, et al. (*165*) found that the severity of aortic atherosclerosis, as measured both by intensity and duration, increased with increasing use of cigarettes and that this dose-relationship persisted when the patients were matched for the consumption of alcohol. On the other hand, Viel, et al. (*200*) concluded from their study of accidental deaths in Chile that "no relationship between atherosclerotic lesions and the use of tobacco was discernible." Examination of the data (provided in graph form only) indicates that heavy smokers showed consistently higher percentages of diseased areas than nonsmokers, but apparently these differences were not statistically significant when subjected to an analysis of variance.

Thus, in addition to the acute effects which smoking exerts on cardiovascular physiology, cigarette smoking is associated with a significant increase in atherosclerosis.

(175) SPAIN, D. M., BRADESS, V. A. Sudden death from coronary heart disease. Survival time, frequency of thrombi, and cigarette smoking. Chest 58(2): 107–110, August 1970.

(12) AUERBACH, O., HAMMOND, E. C., GARFINKEL, L. Smoking in relation to atherosclerosis of the coronary arteries. New England Journal of Medicine 273(15): 775–779, October 7, 1965.

(13) AVTANDILOV, G. G., KOLENOVA, V. I., PONOMARENKO, O. V. Kureniye tabaka i stepen' ateroskleroticheskogo porazheniya koronarnykh arteriy serdtsa i aorty. (Tobacco smoking and the degree of atherosclerotic lesions of coronary arteries of the heart and aorta.) Kardiologiya 5(1): 30–34, January-February 1965.

(165) SACKETT, D. L., GIBSON, R. W., EROSS, I. D. J., PICKREN, J. W. Relation between aortic atherosclerosis and the use of cigarette and alcohol. An autopsy study. New England Journal of Medicine 270(26): [illegible]

(182) STRONG, J. P., RICHARDS, M. L., MCGILL, H. C., JR., EGGEN, D. A., MCMURRAY, M. T. On the association of cigarette smoking with coronary and aortic atherosclerosis. Journal of Atherosclerosis Research 10(3): 303–317, November–December 1969.

(200) VIEL, B., DONOSO, S., SALCEDO, D. Coronary atherosclerosis in person dying violently. Archives of Internal Medicine 122(2): 97–103, August 1963.

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Interpretation of Sudden Deaths. The interpretation of (175) Spain and Bradess is different from the original one by the authors. The last paragraph in the Discussion should be noted.

Discussion

The current findings of an increase in frequency of coronary thrombi with an increase in duration of survival from the onset of the clinical manifestations of the coronary heart attack are almost identical with those of the study reported in 1961.[8] Regardless of the interpretation of these findings, the fact that the results are identical in studies performed almost ten years apart would support the validity of these observations. The concept that some mechanism other than that the formation of a new thrombus triggers the onset of many coronary heart attacks is again restated and that it is during the early phases of this "attack," in progress, that arrhythmias or metabolic deficiencies in the myocardium disturb the hemodynamics of an already embarrassed coronary circulation to favor the formation of a thrombus in a vessel previously compromised by atherosclerosis. This additional obstruction to the circulation enhances the ischemia sufficiently to now produce a transmural infarct which otherwise might not have developed. With increasing time of survival and with the persistence of a myocardial metabolic disturbance and arrhythmia, there is a greater opportunity for such thrombi to develop. In this connection it is pertinent to note that in an experimental study on calves the induction of prolonged ventricular fibrillation was accompanied by massive subendocardial damage.[9] No thrombi were present and the severity of the myocardial lesions increased with the duration of the experiment.

With presently available autopsy techniques it is difficult if not impossible to obtain additional information for further support for the concept of the secondary origin of many coronary thrombi. Autopsies unfortunately provide only one still picture of a process which during life is rapidly evolving, changing and dynamic. The cause often cannot be distinguished from effect. If there is to be confirmation or rejection of this concept it may have to await the time when there will be enough cases from the mobile coronary care unit experiences, who have been treated within the first 30 minutes of the onset of the attack and who have survived for a sufficient length of time. It will then be possible to determine whether these survivors reveal greater or lesser numbers of transmural infarcts than anticipated from experience previously. A significant decrease in this type of infarct which is usually associated with coronary thrombi would contribute important support for the concept of a secondary development of the thrombus after the onset of the attack. This would provide early encouragement for intervention in an attempt to interrupt those processes favoring the formation of thrombi.

The findings also support the view that cigarette smoking exerts some if not its major harmful effects on the acute clinical event rather than on the chronic atherogenic process. The fact that fewer coronary thrombi were present in the more than one pack per day cigarette smokers can be explained by the observation that these are the very cases with the shortest survival and the number of thrombi are noted to increase with longer survival.

The cases in this study were drawn from an overall group of 500 consecutive Medical Examiner autopsies. The smoking history questionnaires had been sent to the next of kin in all of these cases. There were 60 percent respondents. However, the age distribution, sex ratio and causes of death were similar in the autopsies with respondents and nonrespondents. The frequency of coronary thrombi and duration of survival from onset of "attack" were also similar in the respondent and nonrespondent groups. The smoking patterns of the Medical Examiner population as whole in the respondent group showed a ratio of 1 nonsmoker to 1.3 more than 20 cigarettes per day smokers. The ratio in the population from which the Brookdale Hospital autopsies were drawn was 1 nonsmoker to every 1.4 more than 20 cigarettes per day smokers. However, it should be noted that no smoking comparisons were made in the study with the group that survived more than eight hours. Unfortunately, the nature of the problem precludes sufficient numbers of more than eight hour survivors from a Medical Examiner case study as they are admitted to the hospital and therefore upon death do not become Medical Examiner cases. At any rate, the selected population upon which this study was of necessity based, precludes the unconditional generalization of these findings to the population at large.

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TABLE 19.—*Autopsy studies of atherosclerosis*

(Figures in parentheses are number of individuals in that smoking category)[1]

[SM = smokers NS = nonsmokers]

Author, year, country, reference	Autopsy population	Data collection	Cigarettes per day	Severity of aortic sclerosis: Above average	Average	Below average	Conclusions	Comments
Wilens and Plair, 1962, U.S.A. (*214*).	959 consecutive male autopsies at New York City VA hospitals.	Routine clinical records of previous and present admissions.	NS ..... 9.9(161)		40.2	29.8	The authors conclude that in 60 percent of cases, the degree of sclerosis at autopsy was commensurate with age of patient, regardless of smoking habits. In the remaining 40 percent there is evidence that cigarette smoking may be associated with an above-average degree of aortic sclerosis.	Smoking data unavailable for 120 cases. Each aorta specimen given an "atherosclerotic age" by comparison with a standard. If "atherosclerotic age" was found to be 10 years more than real age, the aorta was said to show above-average sclerosis. †$p<0.001$ comparing 9.9 with 25.1 and 29.8 with 13.6.
			<20 ..... 19.1(152)		63.2	17.6		
			20–39 ..... 26.4(268)		62.5	11.1		
			>39 .....†28.1(199)		61.3	†13.6		

(*214*) WILENS, S. L., PLAIR, C. M. Cigarette smoking and arteriosclerosis. Science 138: 975–977, November 30, 1962.

Author, year, country, reference	Autopsy population	Data collection	Degree of coronary artery atherosclerosis (overall age-adjusted results): No atherosclerosis	Slight	Moderate	Advanced	Conclusions	Comments
Auerbach, et al., 1963, U.S.A. (*18*).	1,372 autopsies of male patients in Orange, New Jersey, VA — hospital for whom smoking habit data were available and who did not have overt CHD at death.	Interview with next of kin.	NS 5.6 (69)	57.8	21.8	14.3	The authors conclude that the percentage of men with an advanced degree of coronary atherosclerosis was higher among cigarette smokers than among nonsmokers and that the percentage increased with amount of cigarette smoking. This relationship persisted even when cases were matched for age and cause of death.	
			Current cigarette					
			<20 .....2.6(129)	30.9	37.8	29.2		
			20–39 ....0.8(299)	19.7	42.1	37.4		
			>40 .....0.6(144)	16.1	38.4	45.8		

[1] Unless otherwise specified, disparities between the total number of individuals and the sum of the individual smoking categories are due to the exclusion of either occasional, miscellaneous, mixed, or ex-smokers.

(Figures in parentheses are number of individuals in that smoking category)[1]

[SM = smokers NS = nonsmokers]

Author, year, country, reference	Autopsy population	Data collection	Cigarettes per day: Comparative size of mean area of atherosclerotic lesions in inner coat of coronary arteries. Right coronary artery: SM	NS	Left coronary artery: SM	NS	Conclusions	Comments
Avtandilov, 1965, Russia (*13*).	259 male and 141 female autopsies.	Not specified, but there were: 180 SM and 220 NS.	30–39 ..†15.5(10)	1.3(32)	†3.3	3.2	The author concludes that the worst changes were found in the left and right coronary arteries with less severe changes in circumflex artery and aorta.	Causes of death 96-atherosclerotic, 102-accidental, 202-various diseases. †T-test for significance of difference between means is significant at $p<0.05$ level.
			40–49 ..†23.6(34)	11.5(27)	†15.8	4.4		
			50–59 ..†26.2(39)	14.9(33)	†27.9	9.9		
			60–69 ..†31.9(52)	23.8(35)	†26.5	22.5		
			70–79 .. 41.9(18)	11.7(36)	26.1	15.8		
Sackett, et al., 1968, U.S.A. (*165*).	893 total, including 433 male and 450 female (white) patients autopsied at Roswell Park Memorial Hospital. Represents all deaths 1956–1964 exclusive of 51 male pipe and cigar smokers and 65 incomplete files.	Patient interview on admission.	The results concerning aortic atherosclerosis are given in form of figure presentation of ridit-analysis.				The authors conclude that among males, "... a large increase in the severity of aortic atherosclerosis occurred in the groups using either cigarettes only or both cigarettes and alcohol as compared with the group using neither cigarettes nor alcohol ... there was only a small and statistically insignificant difference between the group using cigarettes alone and the group using both cigarettes and alcohol, ..." The severity of aortic atherosclerosis increased with increasing use of cigarettes, when measured both by intensity and by duration of smoking.	

[1] Unless otherwise specified, disparities between the total number of individuals and the sum of the individual smoking categories are due to the exclusion of either occasional, miscellaneous, mixed, or ex-smokers.

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Coronary Blood Flow

Studies in animals and humans (tables A20, A21) have noted alterations in coronary blood flow (CBF) following the inhalation of cigarette smoke or the administration of nicotine. Generally, exposure of the normal subject to these agents results in an increase in flow. Kien and Sherrod (*112*), Leb, et al. (*126*), Ross and Blesa (*160*), Travell, et al. (*189*), and West et al. (*208*), working with normal animals, and Bargeron, et al. (*17*), working with normal humans, have demonstrated this response. As with the other cardiac responses to the administration of nicotine, it has been found that the augmentation in CBF is most probably due to the release of catecholamines. Using instantaneous coronary arterial flow measurement in dogs, Ross and Blesa (*160*) were able to reproduce the effects of intracoronary nicotine with the administration of epinephrine and were able to block the response to nicotine by pretreatment with pentolinium.

The direct action of catecholamines on the coronary arteries may not, however, be solely responsible for the increase in CBF seen with cigarette smoking and intravenous nicotine administration. It appears that the catecholamine-induced increase in myocardial work and therefore in myocardial oxygen requirement is a prerequisite for the increase in CBF. Kien and Sherrod (*112*), using tracheostomized dogs, found that without blood pressure and cardiac output changes CBF did not increase following either the inhalation of cigarette smoke or the administration of nicotine intravenously, although CBF did increase following such changes. Recent work by Leb, et al. (*126*) has utilized Rb^{86} as a radioactive marker in order to distinguish capillary flow from overall total CBF. The authors consider that this capillary flow represents that portion of CBF which is effectively involved in nutrient and oxygen exchange. The researchers observed that the increase in effective coronary flow was almost proportional to the nicotine-induced increase in myocardial oxygen consumption. However, the increase in total coronary flow which may be due to increased myocardial shunting was far in excess. Thus, the increased work evoked by the effect of nicotine on the myocardium may induce local hormonal release in the myocardium and coronary vessels leading to coronary vasodilatation and increased CBF.

This homeostatic response to increased work appears to be fully effective only in the subjects with normal coronary arteries. Bellet, et al. (*22*), working with normal dogs and dogs that had undergone either coronary artery ligation or artificially-induced coronary artery narrowing, noted that the increase in CBF following the intravenous administration of nicotine was significantly less among the animals with coronary insufficiency. Work with humans discussed above has revealed a similar increase in CBF with smoking in normals. Regan, et al. (*154*) studied seven men with EKG-proven myocardial infarction and observed that cigarette smoke evoked slight increases in myocardial oxygen consumption in only three patients and caused no overall rise in CBF. A number of other investigators have noted that patients with overt CHD do not respond to the stimulus of cigarette smoke as readily as do normals (*67, 149, 164*).

Thus, patients with compromised coronary circulation may not be capable of increasing their coronary flow in the face of the increased demands of a myocardium stimulated by nicotine or cigarette smoke. In the normal state, the heart responds to increased oxygen demands by increasing coronary flow because even at rest oxygen extraction is almost at a maximal level. Any further increase in extraction may produce coronary sinus pO_2 values incompatible with proper tissue oxygenation.

(126) Leb, G., Dernti, F., Robin, E., Bing, R. J. The effect of nicotine on effective and total coronary blood flow in the anesthetized closed-chest dog. Journal of Pharmacology and Experimental Therapeutics 173 (1): 138–141, May 1970.

(189) Travell, J., Rinzler, S. H., Karp, D. Cardiac effects of nicotine in the rabbit with experimental coronary atherosclerosis. Annals of the New York Academy of Sciences 90(1): 290–301, September 27, 1960.

(17) Bargeron, L. M., Jr., Ehmke, D., Conlubol, F., Castellanos, A., Siegel, A., Bing, R. J. Effect of cigarette smoking on coronary blood flow and myocardial metabolism. Circulation 15: 251–257, February 1957.

(22) Bellet, S., West, J. W., Muller, O. F., Manzoli, U. C. Effect of nicotine on the coronary blood flow and related circulatory parameters. Correlative study in normal dogs and dogs with coronary insufficiency. Circulation Research 10(1): 27–34, January 1962.

(154) Regan, T. J., Hellems, H. K., Bing, R. J. Effect of cigarette smoking on coronary circulation and cardiac work in patients with arteriosclerotic coronary disease. Annals of the New York Academy of Sciences 90(1): 186–189, September 27, 1960.

(67) Frankl, W. S., Winters, W. L., Soloff, L. A. The effects of smoking on the cardiac output at rest and during exercise in patients with healed myocardial infarction. Circulation 31(1): 42–44, January 1965.

(149) Pentecost, B., Shillingford, J. The acute effects of smoking on myocardial performance in patients with coronary arterial disease. British Heart Journal 26: 422–429, 1964.

(164) Russek, H. I., Zohman, B. L., Dorset, V. J. Effects of tobacco and whiskey on the cardiovascular system. Journal of the American Medical Association 157(7): 563–568, February 12, 1955.

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Nicotine on Coronary Blood Flow. In this section on Coronary Blood Flow, the effects of cigarette smoking or nicotine injection on canine or human subjects are described together, ignoring the differences between them. After describing the conclusion of (126) Leb et al., a concept is described which states that nicotine increases cardiac work directly, which may in turn induce the release of catecholamines. Leb et al. did not propose such a scheme and nobody else has until the appearance of the 1971 document.

Our results show that myocardial oxygen consumption increases after nicotine administration; this occurs as left ventricular work rises. It was shown previously that nicotine augments the contractile state of the myocardium (Puri *et al.*, 1968). The increase in myocardial oxygen consumption is expected, since the drug augments the contractile state of the heart and cardiac work (Sonnenblick *et al.*, 1968). As a result, the increase in myocardial oxygen demands are met by an increase in the effective coronary flow. Figure 1 shows that capillary flow increases almost proportionally to myocardial oxygen consumption, whereas the increase in total coronary flow is far in excess of myocardial oxygen consumption; this suggests that effective capillary flow measured by this method is more closely related to myocardial oxygen consumption than is total coronary flow.

The results reported here do not permit any conclusions on the exact location of the action of nicotine. It is possible that nicotine, like norepinephrine, decreases coronary vascular resistance (Winbury *et al.*, 1965); this could increase effective coronary flow up to a limit, above which there cannot take place any further rise in effective capillary flow as total coronary flow increases. Only direct observations on the microcirculation similar to those carried out by Wayland *et al.* (1967) will permit more definitive conclusions on this point.

Conclusions. Intravenous administration of nicotine (100 μg/kg in one minute) in the healthy, closed-chest, anesthetized dog caused increases in left ventricular work, in myocardial oxygen consumption and in both effective (nutritional) and total coronary flow.

The increase in effective capillary flow to the myocardium after nicotine administration was sufficient to meet myocardial oxygen demands. Effective capillary flow appeared to be primarily regulated by myocardial oxygen consumption. The proportional increase in myocardial oxygen consumption and effective capillary flow indicates that the effective capillary flow to the myocardium is closely related to myocardial oxygen supply.

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Carbon monoxide (CO) is a colorless and odorless gas, low levels of which have significant effects on human and animal physiology which are just now beginning to be understood. According to Wynder and Hoffmann (315), it is present in cigarette smoke in concentrations of approximately 2.9 to 5.1 percent. The concentration of CO in smoke is subject to many factors, among them the type of tobacco and the porosity of cigarette paper. The concentration of CO in smoke has been found to increase significantly toward the last puffs of the cigarette.

According to Chevalier, et al. (71), a concentration of approximately 4 percent CO in cigarette smoke will produce alveolar levels of around 0.04 percent which, equilibrated with hemoglobin, result in carboxyhemoglobin (COHb) concentrations of from 3 to 10 percent. A number of investigators have compared COHb levels in smokers and nonsmokers. Goldsmith and Landaw (79) reported the analysis of expired air samples obtained from 3,311 longshoremen. Using a regression analysis, they calculated the concentration of COHb and found that nonsmokers showed levels of 1.2 percent while those smoking over 2 packs per day had levels of 6.8 percent and that smokers of lesser amounts had intermediate levels. Occupational exposure accounted for the mean nonsmokers' level being over 1.0 percent, an unusual finding in comparison with other studies. Kjeldsen (178) interviewed and obtained blood samples from 931 CHD-free smokers and nonsmokers. The mean COHb level for 196 nonsmokers was 0.4 percent while all inhaling smokers had a mean level of 7.3 percent. All 416 cigarette smokers, regardless of inhalation or amount smoked, showed a mean level of 4.0 percent.

Carbon monoxide has many varied and significant effects on human physiology. An overall review of these effects may be found in a discussion by Lilienthal (127), or more recently in an extensive review by the United States Public Health Service National Air Pollution Control Administration (194). Apart from its effects on respiratory and circulatory function, CO has been found to affect certain central nervous system functions adversely. These effects are probably due to interference by CO with the proper oxygenation and oxidative metabolism of the tissue in question.

CO interferes with oxygen transport in a variety of ways. First, the affinity of hemoglobin for CO is approximately 200 times greater than its affinity for oxygen, and thus CO can easily displace oxygen from hemoglobin. Second, CO shifts the oxyhemoglobin dissociation curve. By increasing the avidity with which oxygen is bound by hemoglobin, CO interferes with O_2 release at the tissue level. This is of greatest importance at the tissue level where the oxygen content of the capillary blood has been reduced to approximately 40 percent saturation. Here the shift can substantially decrease the oxygen tension supplying the tissues.

Third, and of more recent note, is the possible interference by CO with the homeostatic mechanism by which 2, 3-diphosphoglycerate (2, 3-DPG) controls the affinity of hemoglobin for oxygen. Bunn and Jandl (34) have recently reviewed the various experiments concerning this glycolytic intermediate. The question of whether the low levels of CO present in the blood of smokers can affect this homeostasis is presently under investigation (29, 143), and firm conclusions cannot be drawn at this time.

Apart from its effect on hemoglobin affinity, CO appears to induce arterial hypoxemia, and this may act as an additional cause of tissue hypoxia. Ayres, et al. (15, 16) observed unexpectedly that exposure of individuals to CO sufficient to raise their levels of COHb to between 5 and 10 percent was associated with a significant fall in arterial pO_2. Greater fall in venous pO_2 was noted, but this was considered secondary to increased tissue extraction. In a recent article, Brody and Coburn (30) suggested that this COHb-induced arterial hypoxemia was due to the interaction of a number of factors. These authors noted that in the presence of veno-arterial shunts or of an imbalance in the ventilation-perfusion ratio, the shift in the oxyhemoglobin dissociation curve increased the alveolar-arterial O_2 gradient and resulted in arterial hypoxemia. The presence of shunts as small as 2 percent of cardiac output as well as of approximately 10 percent COHb was found to cause an increase in the gradient. Such ventilation-perfusion (V/Q) abnormalities have recently been noted even in asymptomatic smokers (see Chapter on Chronic Obstructive Bronchopulmonary Disease). The increased levels of COHb found in the blood of smokers may interact with these V/Q abnormalities to further decrease available oxygen.

(315) WYNDER, E. L., HOFFMANN, D. Tobacco and Tobacco Smoke. Studies in Experimental Carcinogenesis. New York, Academic Press, 1967. 730 pp.

(71) CHEVALIER, R. D., KRUMHOLZ, R. A., ROSS, J. C. Reaction of nonsmokers to carbon monoxide inhalation. Cardiopulmonary responses at rest and during exercise. Journal of the American Medical Association 198(10): 1061-1064, December 5, 1966.

(79) GOLDSMITH, J. R., LANDAW, S. A. Carbon monoxide and human health. Science 162(3860): 1352-1359, December 20, 1968.

(178) KJELDSEN, K. Smoking and Atherosclerosis. Investigations on the significance of the carbon monoxide content in tobacco smoke in atherogenesis. Copenhagen, Munksgaard, 1969. 145 pp.

(127) LILIENTHAL, J. L., JR. Carbon monoxide. Pharmacological Review 2: 324-354, 1950.

(194) U.S. PUBLIC HEALTH SERVICE. NATIONAL AIR POLLUTION CONTROL ADMINISTRATION. Air Quality Criteria for Carbon Monoxide. Washington, U.S. Department of Health, Education and Welfare, National Air Pollution Control Administration Publication No. AP-62, March 1970. 153 pp.

(34) BUNN, H. F., JANDL, J. H. Control of hemoglobin function within the red cell. New England Journal of Medicine 282(25): 1414-1421, June 18, 1970.

(29) BREWER, G. J., EATON, J. W., WEIL, J. V., GROVER, R. F. Studies of red cell glycolysis and interactions with carbon monoxide, smoking, and altitude. Advances in Experimental Medicine and Biology 6: 95-114, 1970.

(143) OSKI, F. A., GOTTLIEB, A. J., MILLER, W. W., DELIVORIA-PAPADOPOULOS, M. The effects of deoxygenation of adult and fetal hemoglobin on the synthesis of red cell 2,3-diphosphoglycerate and its in vivo consequences. Journal of Clinical Investigation 49(2): 400-407, February 1970.

(15) AYRES, S. M., GIANNELLI, S., JR., ARMSTRONG, R. G. Carboxyhemoglobin: Hemodynamic and respiratory responses to small concentrations. Science 149: 193-194, July 9, 1965.

(16) AYRES, S. M., MUELLER, H. S., GREGORY, J. J., GIANNELLI, S., JR., PENNY, J. L. Systemic and myocardial hemodynamic responses to relatively small concentrations of carboxyhemoglobin (COHB). Archives of Environmental Health 18(4): 699-709, April 1969.

(30) BRODY, J. S., COBURN, R. F. Carbon monoxide-induced arterial hypoxemia. Science 164(3885): 1297-1298, June 13, 1969.

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In normal individuals, coronary flow can increase to meet the increased oxygen demands of a stressed myocardium (as that under nicotine stimulation), while in individuals with severe CHD coronary flow cannot respond as readily. In such cases, myocardial oxygen extraction must be increased above the almost maximal extraction found at rest. Any interference with arterial oxygen levels or hemoglobin affinity could very well decrease available oxygen supplies below the level required for proper tissue function. That this occurs is suggested by the experiments discussed below.

Chevalier, et al. (121) exposed 10 young nonsmokers to CO concentrations sufficient to induce COHb levels of approximately 4 percent. Taking measurements from blood specimens obtained at cardiac catheterization under resting and exercise conditions, the authors noted that the ratio of oxygen debt to oxygen uptake increased significantly under conditions of increased COHb. According to the investigators this implied that the same work was being done at a greater metabolic cost. These same authors (121, 122) had previously noted similar findings among smokers and observed that cessation of smoking was associated with a significant improvement in oxygen debt accumulation.

More recent work by Ayres, et al. (15) has focused on the difference in response to CO exposure between 7 normals and 4 patients suffering from CHD (proven arteriographically). The induction of a COHb concentration of approximately 9 percent in the normals was followed by an increase in coronary blood flow, a decrease in hemoglobin-oxygen percent extraction and no change in myocardial oxygen consumption, coronary sinus oxygen tension, and lactate and pyruvate extraction ratios. The induction of similar COHb levels in the CHD patients was followed by no change in coronary blood flow, a decrease in the hemoglobin-oxygen extraction ratio, and no change in myocardial oxygen consumption. However, these patients did manifest a decrease in coronary sinus pO_2 as well as a decrease in lactate and pyruvate extraction. The latter measures indicate that the myocardium was functioning under hypoxic conditions. Because the coronary flow could not increase and because the myocardium could not extract O_2 from arterial O_2 which was under the influence of CO, coronary sinus oxygen tension decreased to a point which could inactivate certain oxidative enzyme processes. Thus, the myocardial function of persons with CHD may be unable to compensate for the stresses induced by smoking.

Although COHb levels resulting from the CO present in the atmosphere during periods of high air pollution are much lower than those due to the inhalation of cigarette smoke, these concentrations of COHb might contribute to the manifestations of CHD. Cohen, et al. (44) studied the case fatality rates for patients admitted to 35 Los Angeles area hospitals with myocardial infarction in relation to atmospheric CO pollution. The authors observed an increased MI case fatality rate in areas of increased pollution, and seen only during periods of relatively increased CO pollution.

An area of interest which has been discussed in previous reports concerns the presence of hydrogen cyanide in tobacco smoke. According to Wynder and Hoffmann (215), the amount present ranges from 11 to 32 micrograms HCN per puff. It is known that a significant amount of this material is detoxified to thiocyanate and excreted as such in the urine or saliva. However, cyanide is a potent inhibitor of oxidative metabolism. Such inhibition of myocardial oxidative metabolism may be of importance when combined with the other factors mentioned above which tend to decrease the oxygen supply available and increase the need for oxygen on the part of the myocardium.

(121) KRUMHOLZ, R. A., CHEVALIER, R. B., ROSS, J. C. Cardiopulmonary function in young smokers. A comparison of pulmonary function measurements and some cardiopulmonary responses to exercise between a group of young smokers and a comparable group of nonsmokers. Annals of Internal Medicine 60(4): 603–610, April 1964.

(122) KRUMHOLZ, R. A., CHEVALIER, R. B., ROSS, J. C. Changes in cardiopulmonary functions related to abstinence from smoking. Studies in young cigarette smokers at rest and exercise at 3 and 6 weeks of abstinence. Annals of Internal Medicine 62(2): 197–207, February 1965.

(44) COHEN, S. I., DEANE, M., GOLDSMITH, J. R. Carbon monoxide and survival from myocardial infarction. Archives of Environmental Health 19(10): 510–517, October 1969.

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Effects of Smoking on the Formation of Atherosclerotic Lesions

A number of autopsy studies have demonstrated a significant association between cigarette smoking and the presence of aortic and coronary artery atherosclerosis, even in men without a history of clinical CHD. The possible pathophysiologic mechanisms for the atherogenic influence of cigarette smoking are discussed in this section.

A number of investigators have studied the effect of nicotine administration, either subcutaneously or intravenously, upon atherosclerotic changes in the aorta and coronary arteries of animals (table A22). When administered alone, nicotine induces certain necrotic changes in the arterial wall. However, in combination with the administration of increased amounts of cholesterol in the diet, nicotine aggravates either subendothelial fibrosis (*75*) or definite atheromatous lesions (*36, 75, 80, 130, 178*). Studies by Choi (*42*) and by Wenzel, et al. (*207*) did not demonstrate this synergism between cholesterol and nicotine.

The other major cigarette smoke component under discussion in this chapter, carbon monoxide, has also been recently implicated in atherogenesis. Table 24 presents the studies which have related exposure to CO in combination with increased dietary cholesterol to both macroscopic and microscopic aortic and coronary atheromatosis. Astrup, et al. (*10*) exposed cholesterol-fed rabbits to CO continually over a period of up to 10 weeks. The experimental group showed increased aortic atheromatosis over that shown by the control group, also cholesterol-fed. Kjeldsen, et al. (*114*) observed that exposure of rabbits to increased oxygen concentrations significantly reduced the amount of cholesterol-induced atheromatosis in rabbits. Most recently, Webster, et al. (*204*) have extended this research to primates. These investigators found that cholesterol-fed squirrel monkeys developed significantly more coronary artery atherosclerosis when exposed intermittently to CO over a 7-month period than when exposed only to room air.

Recent discussion has centered on the mechanisms whereby CO can induce these changes (*9, 212*). Astrup (*9*), referring to previous experiments in humans which had shown increased vascular permeability for albumin upon chronic exposure to CO (*11*), considers it likely that this increase in permeability allows for increased filtration of lipoproteins into arterial walls. This, he considers, is a primary cause of intimal and medial lipid accumulation and, therefore, of atherosclerosis.

Another point of view has been stressed by Whereat (*212*), who considers the filtration theory to be an inadequate hypothesis for mural lipid accumulation. The author notes that when the oxidation of the pyridine nucleotide, nicotinamideadenine dinucleotide (NAD), is impaired, the reduced form of this nucleotide (NADH) provides an essential factor for fatty acid synthesis. Fatty acid synthesis in the aorta and heart is carried out by mitochondrial enzymes whose hydrogen donor is NADH. Substances which slow or impair the reoxidation of this compound tend to increase mitochondrial fatty acid synthesis (and decrease fatty acid utilization) in the arterial wall. Carbon monoxide prevents this oxidation process both directly and indirectly. Indirectly, it decreases the oxygen available for diffusion into the tissue. Directly, carbon monoxide can stall the process of NADH oxidation by combining with cytochrome oxidase. Further research is required into this problem, particularly in view of the fact that cyanide is also a respiratory chain inhibitor and thus may also adversely affect arterial wall fat metabolism.

(75) Grosgogeat, Y., Anguera, G., Lellouch, J., Jacotot, B., Beaumont, J.-L., Patois, E., Manier, E. L'intoxication chronique par la nicotine chez le lapin nourri au cholesterol. Effets sur la paroi aortique et sur la lipidemie. (Chronic nicotine poisoning in the rabbit on a cholesterol diet. Effects on the wall of the aorta and on lipidemia.) Journal of Atherosclerosis Research 5(2): 291–301, 1965.

(36) Czochra-Lysanowicz, Z., Gorski, M., Kedra, M. Wplyw nikotyny i kofeiny na rozwoj miazdzycy u krolikow. (The effect of nicotine and caffeine on the development of arteriosclerosis in rabbits.) Annales Universitatis Mariae Curie-Sklodowska; Section D: Medicina 14(20): 181–206, 1959.

(80) Kass, G. M., Landenholm, W., Hemmens, A. Production of calcific athero-arteriosclerosis and thromboarteritis with nicotine, vitamin D, and dietary cholesterol. American Journal of Pathology 49(4): 739–771, October 1966.

(130) Maslova, K. K. The influence of nicotine on experimental atherosclerosis. Bulletin of Experimental Biology and Medicine 41: 20–23, 1956.

(178) Stefanovich, V., Gore, I., Kajiyama, G., Iwanaga, Y. The effect of nicotine on dietary atherogenesis in rabbits. Experimental and Molecular Pathology 11(1): 71–81, August 1969.

(42) Choi, Y. Y. Effect of nicotine upon cholesterol-induced atherosclerosis in rabbits. New Medical Journal 10(7): 685–693, 1967.

(207) Wenzel, D. G., Turner, J. A., Kissil, D. Effect of nicotine on cholesterol-induced atherosclerosis in the rabbit. Circulation Research 7: 256–261, March 1959.

(10) Astrup, P., Kjeldsen, K., Wanstrup, J. Enhancing influence of carbon monoxide on the development of atheromatosis in cholesterol-fed rabbits. Journal of Atherosclerosis Research 7: 343–354, 1967.

(114) Kjeldsen, K., Astrup, P., Wanstrup, J. Reversal of rabbit atheromatosis by hyperoxia. Journal of Atherosclerosis Research 10(2): 173–178, September-October 1969.

(204) Webster, W. S., Clarkson, T. B., Lofland, H. B. Carbon monoxide-aggravated atherosclerosis in the squirrel monkey. Experimental and Molecular Pathology 13(1): 36–50, 1970.

(9) Astrup, P. Effects of hypoxia and of carbon monoxide exposures on experimental atherosclerosis. Annals of Internal Medicine 71(2): 426–427, August 1969.

(212) Whereat, A. F. Is atherosclerosis a disorder of intramitochondrial respiration? Annals of Internal Medicine 73(1): 125–127, July 1970.

(11) Astrup, P., Pauli, H. G. (Editors). A Comparison of Prolonged Exposure to Carbon Monoxide and Hypoxia in Man. Reports of a Joint Danish-Swiss Study. Scandinavian Journal of Clinical and Laboratory Investigation 22 (Supplement 103): 1968. 71 pp.

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Atherosclerotic Lesions in the Rabbit. The conflicting results reported by (207) Wenzel et al. and (178) Stefanovich et al. need some explanation because the emphasis differs between the two. Wenzel, in addition to gross examination of the aorta also stressed the animal with ergonovine to induce abnormalities in the ECG. Stefanovich analyzed cholesterol in the aorta and found that the level was lower in the nicotine treated rabbit. There are numerous problems in using cholesterol fed rabbits, yet this is the animal which serves as the basis for the claim that smoking causes atherosclerosis. Note the differences in conclusions between Wenzel (top) and Stefanovich (bottom).

SUMMARY

Rabbits (New Zealand, albino, females) on a cholesterol (1%) diet and injected with nicotine (2.78 mg/kg 5 days a week for 6 weeks) demonstrated wider areas of involvement of the intima (19.4% vs. 5.7%) in the aorta than rabbits on a cholesterol diet alone. In both *stock*-fed and cholesterol-fed animals, nicotine produced an increase in aortic triglycerides and a decrease in the free cholesterol content. An increase in phospholipids, particularly in lecithin and cephalin, was observed in the cholesterol-fed rabbits treated with nicotine. Aortic acid mucopolysaccharide composition did not exhibit any significant changes following nicotine treatment.

In experiments *in vitro*, it was shown that heparin and nicotine form a relatively stable complex, in a molar ratio of about 1:20; nicotine also inhibits the hydrolysis of ^{14}C-labeled triolein in a homogenate from rabbit aortic tissue. It is suggested that some of the biological effects of nicotine may be the result of a complex formation between nicotine and heparin *in vivo*.

SUMMARY

Groups of female albino rabbits [illegible] administered cholesterol, nicotine, and [illegible] cholesterol for a 24 week period. [illegible] addition of nicotine to the cholesterol regimen did not significantly affect body weight, [illegible] cholesterol or lipid phosphorus or gross atherosclerosis under the conditions of this test. The nicotine-cholesterol group demonstrated greater mortality, as well as greater electrocardiographic and pathologic evidence of cardiac involvement and peripheral vascular changes, than did the cholesterol or nicotine groups. It is suggested that the combination of nicotine and cholesterol produces a cardiovascular interaction.

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The Effect of Smoking on Thrombosis

In the study of CHD, a number of investigators have turned their attention to thrombosis because myocardial infarction and sudden coronary death frequently result from thrombotic events. A thrombus may be of either gross or microscopic dimensions, and a minute thrombus at a strategic site may precipitate a fatal arrhythmia. However, thrombotic and prethrombotic states are difficult to detect except when gross, and the emphasis has been primarily on factors which can be studied conveniently. Coagulation is now thought to have a secondary role in the consolidation of an arterial thrombus and little if any in initiating the process. The prime mechanism in thrombogenesis appears to be the reaction of the platelet. Several papers have been written about platelet reactivity *in vitro* but few about the effect of smoking on platelet behavior *in vivo*. The assay of fibrinolysis, which may also be important, has received scanty treatment. The relevant studies are listed in table A27. Many of these are discussed in the 1968 supplement (*192*) and by Murphy (*110*). Corroborative data are still unconclusive as to whether smoking shortens platelet survival.

(110) Murphy, E. A. Thrombozyten, Thrombose und Gerinnung. (Thrombocytes, thrombosis and clotting.) IN: Schievelbein, H. (Editor). Nikotin: Pharmakologie und Toxikologie des Tabakrauches. Stuttgart (West Germany), Georg Thieme Verlag, 1968. pp. 178–192.

The Effect of Smoking on Serum Lipid Levels

In the discussion concerning the epidemiological aspects of CHD, it was noted that increased serum cholesterol was a significant risk factor for the development of overt CHD. Serum triglycerides have also been related to CHD incidence. Of concern also is the immediate effect which cigarette smoking has upon blood lipid levels.

The studies concerning this immediate effect are presented in tables A 25 and A 25a. The table is divided into a section concerning studies on humans (table A 25) and one concerning studies utilizing animals or *in vitro* systems (table A 25a). Although no consistent response was noted for serum cholesterol, serum free fatty acids were found consistently to rise following smoking. As with other cardiovascular reactions to nicotine and smoking, it appears that the fatty acid response is also mediated by catecholamine release. This relationship has been observed in a number of experiments by Kershbaum, et al. (*105, 106, 108, 109, 110*) and Klensch (*118*). That nicotine is primarily responsible for this rise may be seen by reference to the study by Kershbaum, et al. (*105*) in which lettuce-leaf cigarettes of minimal nicotine content had a negligible effect upon serum free fatty acids in comparison with that of regular cigarettes.

While attention has been centered upon nicotine as the agent inducing the immediate increase in serum lipids, recent studies have been concerned with the effect of chronic exposure to carbon monoxide on serum lipid metabolism. These studies are listed in table A 26. Among rabbits fed increased amounts of cholesterol, the authors observed significant increases in cholesterol and triglyceride concentrations in those exposed to CO versus those maintained in a normal atmosphere.

(105) Kershbaum, A., Bellet, S., Hirabayashi, M., Feinberg, L. J. Regular filtertip, and modified cigarettes. Nicotine excretion, free fatty acid mobilization and catecholamine excretion. Journal of the American Medical Association 201(7): 545–546, August 14, 1967.

(106) Kershbaum, A., Bellet, S., Jimenez, J., Feinberg, L. J. Differences in effects of cigar and cigarette smoking on free fatty acid mobilization and catecholamine excretion. Journal of the American Medical Association 195(13): 1095–1098, March 28, 1966.

(108) Kershbaum, A., Jimenez, J., Bellet, S., Zanettini, D. Modification of nicotine-induced hyperlipidemia by anti-adrenergic agents. Journal of Atherosclerosis Research 6: 524–530, 1966.

(109) Kershbaum, A., Khorsandian, R., Caplan, R. F., Bellet, S., Feinberg, L. J. The role of catecholamines in the free fatty acid response of cigarette smoking. Circulation 28(1): 52–57, July 1963.

(110) Kershbaum, A., Osada, H., Scriabine, A., Bellet, S., Pappas, D. J. Influence of nicotine on the mobilization of free fatty acids from rat adipose tissue *in vitro* and in the isolated perfused dog limb. Circulation 36(4, Supplement 2): 20, October 1967.

(118) Klensch, H. Blut-Katecholamine und -Fettsäuren beim Stress durch Rauchen und durch körperliche Arbeit. (Blood catecholamines and fatty acids under stress induced by smoke and exercise.) Zeitschrift für Kreislaufforschung 55(10): 1035–1044, October 1966.

Other Areas of Investigation

Certain other aspects of cardiovascular pathophysiology may be of importance in the relationship of smoking to CHD. Glucose metabolism and insulin response, when altered, may alter myocardial response. This topic has been covered in detail in the 1968 Supplement to the Health Consequences of Smoking (*192*). Also, variations in blood hemoglobin and hematocrit may adversely affect coronary blood flow. A number of studies showing a possible relationship of smoking to hemoconcentration have been reviewed previously (*191, 192*), and the reader is referred to those discussions.

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Cerebrovascular Disease

The term cerebrovascular disease (CVD) refers to a number of different types of vascular lesions affecting the central nervous system: subarachnoid hemorrhage, cerebral hemorrhage, cerebral embolism, and thrombosis (ICD Codes 330 to 334). In 1967 in the United States, a total of 93,071 males and 109,113 females were listed as dying from CVD as the underlying cause (*196*).

Epidemiological studies indicate that cigarette smoking is associated with increased mortality from cerebrovascular disease, whether CVD is listed as the underlying or as a contributory cause of death. Table 28 presents the results of the seven major epidemiological studies. The smoking of pipes and cigars does not appear to increase significantly the risk of dying from CVD. The importance of high blood pressure and diabetes as risk factors for mortality from CVD has recently been noted by Hammond and Garfinkel (*76*). The data from their study, as presented in table 28, also indicate that the mortality ratio for cigarette smokers is greater for persons under 75 years of age than for older individuals.

Many of the pathophysiological considerations discussed in the sections concerning CHD may also pertain to the relationship of smoking and CVD, particularly cerebral infarction.

In a study reported by Kuhn (*122*), 20 habitual smokers refrained from smoking for one-half day, and base line retrograde brachiocerebral angiograms were taken; they then smoked one cigarette, inhaling deeply, and had repeat angiograms. Those over 60 years of age failed to have significant acceleration of flow as demonstrated in carbon dioxide inhalation experiments.

More recently, Miyazaki (*132*) studied the effect of smoking on the cerebral circulation of 12 moderate/heavy cigarette smokers as measured indirectly using an ultrasonic Doppler technique to record internal carotid artery flow. Measurements were made before and after ordinary smoking and showed an increase in cerebral blood flow and a decrease in cerebral vascular resistance in all subjects. No significant difference in response was observed between the 4 younger and 8 older (over 60 years of age) subjects. More research is needed to clarify the role of cigarette smoking in the acute pathogenesis of CVD manifestations. However, the chronic effect of smoking upon the cerebral circulation (particularly its extracranial portion) is likely to be similar to the effect of smoking upon the aortic and coronary atherosclerosis.

Non-Syphilitic Aortic Aneurysm

Aortic aneurysm is an uncommon but not rare cause of death. In 1967 in the United States, a total of 8,448 men and 3,173 women were listed as dying from aortic aneurysm as the underlying cause (*196*). Cigarette smoking appears to increase the risk of dying from this disease, perhaps by promoting the atherosclerotic process which underlies this type of aneurysm. As illustrated in table 29, the mortality ratios for cigarette smokers are high relative to other cardiovascular diseases in which smoking increases the risk, and the risk increases in proportion to the amount smoked.

(122) Kuhn, R. A. Mode of action of tobacco smoke inhalation upon the cerebral circulation. Annals of the New York Academy of Sciences 142 (Article 1): 67-71, March 15, 1967.

(132) Miyazaki, M. Circulatory effect of cigarette smoking, with special reference to the effect on cerebral hemodynamics. Japanese Circulation Journal 33(9): 907-912, September 1969.

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TABLE 24.—*Experiments concerning the atherogenic effect of carbon monoxide exposure and hypoxia*

Author, year, country, reference	Number and type of animal	Procedure	Results
Astrup et al., 1967 Denmark (10).	24 female albino rabbits.	Regular diet plus 2 percent cholesterol: I. (12) control. II. (12) continual exposure to carbon monoxide: 0.017 percent for 8 weeks. 0.035 percent for 2 weeks.	The experimental group exposed to carbon monoxide showed increased macro- and microscopic aortic atheromatosis over that shown by control animals. Microscopic examination revealed intimal lipoid deposition limited in penetration by the internal elastic membrane. Coronary vessels were found to show similar changes. Carboxyhemoglobin (COHb) levels averaged 15–17 percent during the first 6 weeks and 33 percent during the final 2 weeks.
Kjeldsen et al., 1968, Denmark (117).	24 castrated male albino rabbits.	Regular diet plus 2 percent cholesterol: I. (12) control. II. (12) continual exposure to hypoxia: 10 percent O_2 for 6 weeks. 8 percent O_2 for 2 weeks.	The experimental group exposed to hypoxia showed increased macroscopic aortic atheromatosis over that shown by control animals. Microscopic examination revealed more intimal and subintimal lipid deposition in the aortas of the exposed rabbits than in those of the nonexposed. The total amount of cholesterol deposited in the aortas of the experimental group was three times higher than in those of the control group.
Kjeldsen et al., 1969, Denmark (114).	24 castrated male albino rabbits.	Regular diet plus 2 percent cholesterol: I. (12) control. II. (12) exposure to 23 percent O_2 for 10 weeks.	Macroscopically, the experimental group showed significantly fewer atheromatous changes. Microscopically, the experimental group showed significantly less aortic intimal lipid deposition.
Webster et al., 1970, U.S.A. (204).	22 female squirrel monkeys.	Diet containing 0.5 percent cholesterol and 25 percent fat: I. (10) control. II. (12) experimentally exposed to 200–300 p.p.m. carbon monoxide for 20 hours per week for 7 months.	The experimental group exposed to carbon monoxide showed a greater mean percentage of coronary arteries with atherosclerotic lesions and more lumen occlusion among the affected arteries. There were significantly more CO-treated monkeys than control monkeys having 35 percent or more apparent atherosclerotic stenosis among the affected arteries. Aortic atherosclerosis was apparently not aggravated by exposure to CO. COHb levels at the end of each exposure period averaged 16–26 percent during the final 24 weeks of the experiment.

(117) KJELDSEN, K., WANSTRUP, J., ASTRUP, P. Enhancing influence of arterial hypoxia on the development of atheromatosis in cholesterol-fed rabbits. Journal of Atherosclerosis Research 8(5): 835–845. 1968.

[illegible]

(Mortality ratio—actual number of deaths shown in parentheses)[1]

[SM = smokers NS = nonsmokers]

PROSPECTIVE STUDIES

Author, year, country, reference	Number and type of population	Data collection	Follow-up years	Number of deaths due to CVD as underlying cause	Cigarettes per day	Pipes and cigars	Age variation	Comments
Hammond and Horn, 1958, U.S.A. (77, 78).	187,783 white males in 9 states 50–69 years of age.	Questionnaire and follow-up of death certificate.	8½	1,050	NS .....1.00 (166) Cigarettes SM .....†1.30 (656) Other SM ..1.25 (230) *Cigarettes only* <10 .....1.24 (41) 10–20 .....1.44 (140) >20 .....1.40 (83)			†($p<0.01$).
Doll and Hill, 1964, Great Britain (50).	Approximately 41,000 male British physicians.	Questionnaire and follow-up of death certificate.	10	606	NS .....1.00 All SM .....1.05 All cigarette 1.12 1–14 .....1.10 15–24 .....1.09 >25 .....1.26			
Kannel et al., 1965 U.S.A. (96).	5,127 males and females 30–59 years of age.	Medical examination and follow-up.	12	13	NS .....1.00 (5) Heavy SM (>20) 3.23 (8)			Data apply only to males 30–59 years of age at entry. Data apply only to cerebral infarction.

[1] Unless otherwise specified, disparities between the total number of deaths and the sum of the individual smoking categories are due to the exclusion of either occasional, miscellaneous, mixed, or ex-smokers.

(96) KANNEL, W. B., DAWBER, T. R., COHEN, M. E., MCNAMARA, P. M. Vascular disease of the brain—epidemiologic aspects. The Framingham study. American Journal of Public Health and the Nation's Health 55(9): 1355–1366, September 1965.

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TABLE 28.—*Deaths from cerebrovascular disease related to smoking (cont.)*

(Mortality ratios—actual number of deaths shown in parentheses)[1]

[SM = smokers NS = nonsmokers]

PROSPECTIVE STUDIES

Author, year, country, reference	Number and type of population	Data collection	Follow-up years	Number of deaths due underlying to CVD as cause	Cigarettes per day	Pipes and cigars	Age variation	Comments
Kahn, 1966, U.S.A. (83).	U.S. male veterans 2,285,674 person years.	Questionnaire and follow-up of death certificate.	8½	2,038	NS .....1.00 (614) All current ....1.30(1,934) Current cigarettes ..1.32 (692) 1–9 .....1.51 (93) 10–20 .....1.42 (325) 21–39 .....1.70 (216) >39 .....1.59 (37)	*Pipes* SM ..1.06 (82) NS ..1.00(614) *Cigars* NS ..1.00(614) SM ..1.03(135)		—
Hammond and Garfinkel, 1969, U.S.A. (76).	358,534 males 465,875 females 40–79 years of age at entry.	Questionnaire and follow-up of death certificate.	6	4,039			*Current regular cigarette* 40–49 50–59 60–69 70–79 *Males* Never smoked 1.00 1.00 1.00 1.00 1–9 .....2.78 1.85 1.30 0.95 10–19 .....1.14 1.48 †1.46 0.92 20–39 .....2.21 2.03 1.62* 1.22 >40 .....1.64 2.40 1.72 †0.66 *Females* Never smoked 1.00 1.00 1.00 1.00 1–9 .....1.53 1.26 1.26 0.83 10–19 .....2.60 2.70 2.15 †0.57 20–39 .....2.93 2.67 1.83 1.28 >40 .....†5.70 †3.52 — —	†Based on only 8–9 deaths.

[1] Unless otherwise specified, disparities between the total number of deaths and the sum of the individual smoking categories are due to the exclusion of either occasional, miscellaneous, mixed, or ex-smokers.

TABLE 28.—*Deaths from cerebrovascular disease related to smoking (cont.)*

(Mortality ratios—actual number of deaths shown in parentheses)[1]

SM = Smokers. NS = Nonsmokers.

PROSPECTIVE STUDIES

Paffenbarger, et al. 1970 U.S.A. (144).	3,263 male longshoremen 35–64 years of age in 1951.	Initial multiphasic screening and follow-up of death certificate.	16	67	NS and <20 .....1.00 (42) >20 .....1.15 (25)		

RETROSPECTIVE STUDY

Paffenbarger and Williams 1967 U.S.A. (145).	>50,000 male University students followed up to 60 years.	Initial college entrance medical examinations with follow-up of death certificate. Controls—surviving classmates age-matched.		*Death Rates* *Cases (158)* *Controls (615)* SM .....45.0 21.3(p<0.01) Cigarette SM >10 per day . 20.9 11.2(p<0.01)		The 63 deaths from occlusive stroke contributed to the statistical significance. The 95 deaths from hemorrhagic stroke showed no statistical significance as a single group.

[1] Unless otherwise specified, disparities between the total number of deaths and the sum of the individual smoking categories are due to the exclusion of either occasional, miscellaneous, mixed, or ex-smokers.

(145) PAFFENBARGER, R. S., JR., WILLIAMS, J. L. Chronic disease in former college students. V. Early precursors of fatal stroke. American Journal of Public Health and the Nation's Health 57(8): 1290–1299, August 1967.

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TABLE 29.—*Deaths from nonsyphilitic aortic aneurysm related to smoking—prospective studies*

(Mortality ratios—actual number of deaths shown in parentheses)[a]

[SM = Smokers NS = Nonsmokers]

Author, year, country, reference	Number and type of population	Data collection	Follow-up years	Number of deaths	Cigarettes per day	Pipes	Cigars	Comments
Hammond and Horn, 1958, U.S.A. (77, 78).	187,783 white males in 9 states 50–69 years of age.	Questionnaire and follow-up of death certificate.	3½	46	NS .....1.00 (25) (expected) SM .....2.12 (44) (p<0.006)			
Kahn, 1968, U.S.A. (85).	U.S. male veterans 2,205,876 person years.	Questionnaire and follow-up of death certificate.	8½	431	NS .....1.00 (55) Current cigarettes ....5.24 (234) 1–9 cigarettes/day ...2.12 (13) 20–29 .....5.53 (124) 21–39 .....5.95 (25) >39 .....7.26 (27)	NS ..1.00 (89) SM ..1.18 (8)	NS ..1.00 (89) SM ..2.00 (24)	
Hammond and Garfinkel, 1969, U.S.A. (76).	359,534 males 445,575 females 40–73 years of age at entry.	Questionnaire and follow-up of death certificate.	6	337	NS .....1.00 1–9 .....2.42 10–19 .....3.85 20–39 .....4.64 >40 .....5.00			Data apply only to males 50–69 years of age.
Weir and Dunn, 1970, U.S.A. (203).	65,153 California male workers 35–64 years of age at entry.	Questionnaire and follow-up of death certificate.	5–8	61	NS .....1.00 ≤5 .....2.64 ≥10 .....2.48 ≥20 .....2.88 ≥30 .....2.64			SM include ex-smokers. NS include pipe and cigar smokers.

[a] Unless otherwise specified, disparities between the total number of deaths and the sum of the individual categories are due to the exclusion of either occasional, miscellaneous, mixed, or ex-smokers.

PERIPHERAL ARTERIOSCLEROSIS

Peripheral arteriosclerosis represents the effects on the vasculature of the extremities of the pathophysiologic processes which produce coronary and aortic atherosclerosis. A number of studies have been concerned with smoking as a risk factor in the development of this disease. Kannel, et al. (*95*) observed, in the Framingham study, that diabetes mellitus and elevated serum cholesterol, as well as cigarette smoking, were also risk factors in the development of peripheral vascular disease.

Juergens, et al. (*92*) reviewed the records of and contacted 478 male patients with arteriosclerosis obliterans (a severe form of peripheral arteriosclerosis), who had been patients at the Mayo Clinic between 1939 and 1948. The diagnosis of this condition was based upon certain clinical criteria: the presence of intermittent claudication, the marked diminution or absence of lower extremity arterial pulsations, and objective trophic manifestations of peripheral limb ischemia. Smoking information was available on 401 patients. These patients were compared with a control group of 350 Mayo Clinic patients of similar age who showed no clinical evidence of vascular disease. It was found, for males under the age of 60, that 2.5 percent of the cases and 25 percent of the controls were nonsmokers. However, no difference was noted between the percentages of heavy smokers in each group. The authors also implicated high blood pressure and elevated serum cholesterol as risk factors in the occurrence of this disease.

Begg (*19*) noted similar findings in a study of 294 male patients with intermittent claudication who were patients at the Western Infirmary in Glasgow, Scotland. In comparing the smoking histories of 100 patients with this complaint with those of 116 healthy male controls, the author found that 1 percent of the patients and 21 percent of the controls had never smoked. A total of 42 percent of the patients smoked more than 20 cigarettes per day while only 24 percent of the controls had a similar history of heavy smoking. The author concluded that smoking, while not a prime cause of peripheral arterial disease, is a significant cofactor in its development in almost all cases. The author also noted obesity, high blood pressure, and elevated serum cholesterol as risk factors.

(*95*) KANNEL, W. B., DAWBER, T. R., SKINNER, J. J., JR., MCNAMARA, [illegible] SHURTLEFF, D. Epidemiological aspects of intermittent claudication: The Framingham Study. Circulation (Supplement II to Vols. 31 [illegible] 32): 121–122, October 1965.

(*92*) JUERGENS, J. L., BARKER, N. W., HINES, E. A., JR. Arteriosclerosis obliterans: Review of 520 cases with special reference to pathogen[illegible] and prognostic factors. Circulation 21(2): 188–195, February 19[illegible]

(*19*) BEGG, T. B. Characteristics of men with intermittent claudica[illegible] Practitioner 194(2): 202–207, February 1965.

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Schwartz, et al. (*168*) compared the prevalence of risk factors in four groups of subjects: 141 cases with arteriosclerotic disease of the lower limbs, 551 cases with coronary arteriosclerosis, 58 cases with both conditions, and finally an indefinite number of control individuals who had been hospitalized for injuries. The investigators reported that certain risk factors, including hypercholesterolemia, hypertension, and cigarette smoking, were significant in both coronary and lower limb arteriosclerosis. The authors noted that the inhalation of cigarette smoke appeared to be an important risk factor for coronary arteriosclerosis up to age 55 while in arteriosclerosis of the lower extremities, inhalation appeared to increase the risk even in the older age groups.

(*168*) Schwartz, D., Lellouch, J., Anguera, G., Richard, J. L., Beaumont, J. L. Etiologie comparee de l'arteriopathie obliterante des membres inferieurs et de l'arteriopathie coronarienne. (Comparative etiology of lower limb obliterative arteriopathy and of coronary arteriopathy.) Archives des Maladies du Coeur 58: Supplement No. 3, 24–32, 1965.

Widmer, et al. (*215*) compared 277 male patients with arterial occlusion of the limbs as demonstrated by aortography or oscillography with 2,082 men demonstrated by oscillography to be free of arterial disease. The authors found that cigarette smoking, particularly heavy smoking, was significantly more frequent among the cases with arterial occlusion than among the controls. Increased beta-lipoproteins and systolic hypertension were also found to be more common among the cases.

(*215*) Widmer, L. K., Hartmann, G., Duchosal, F., Plechl, S.-C. Risk factors in arterial occlusion of the limbs. German Medical Monthly 14 (10): 476–479, October 1969.

Experimental Evidence

A number of experimenters have investigated the acute effects of smoking or nicotine upon the peripheral circulatory system. These investigators, as listed in table A 30, have measured effects in terms of alterations in skin temperature and blood flow as measured by plethysmography, radioactive iodinated albumin clearance, or radiosodium clearance from the skin. The majority of these studies have shown significant decreases in peripheral blood flow and skin temperature upon smoking, particularly in persons without manifest peripheral vascular disease. The study of Freund and Ward (*68*) demonstrates the difference in peripheral vascular reactivity found between normals and patients with arteriosclerotic changes in the vessels of their extremities. The work of Stromblad (*181*) on blockade of this response with automatic system blockers indicates that the reactivity of these vessels is secondary to the local release of catecholamines. Most probably, the degenerative changes associated with this disease create a stiffening of the vessel wall and prevent rapid alteration, particularly dilatation, in response to the catecholamines liberated by smoking or nicotine.

(*68*) Freund, J., Ward, C. The acute effect of cigarette smoking on the digital circulation in health and disease. Annals of the New York Academy of Sciences 90(1): 85–101, September 27, 1960.

(*181*) Stromblad, B. C. R. Effect of intra-arterially administered nicotine on the blood flow in the hand. British Medical Journal 1: 484–435, February 21, 1959.

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Thromboangiitis Obliterans

Thromboangiitis obliterans (Buerger's Disease) (TAO) is an uncommon obstructive vasculitis primarily involving the arteries and veins of the extremities. Severely affected patients may even lose their limbs secondary to ischemic changes. Much discussion has centered upon the question as to whether this disease is a clinical and pathological entity separate from peripheral arteriosclerosis. McKusick, et al. (*123*) consider it to be a distinct entity while Eisen (57) concludes that TAO is the acute inflammatory phase of severe arteriosclerosis.

Clinically, it has been shown that smoking aggravates this disease and cessation of smoking frequently aids in complete or partial remission. Razdan, et al. (*153*) and Brown, et al. (*32*) found very few nonsmokers in groups of patients diagnosed as having typical TAO. A recent study from Israel (*16*) involved a case-control comparison of 46 patients with TAO and 32 matched controls. Although the controls were found to smoke less per day than the patients, this difference was not found to be statistically significant. However, 100 percent of the smoking patients and only 72 percent of the smoking controls were inhalers, a difference significant at the 0.02 level.

(*123*) McKusick, V. A., Harris, W. S., Ottesen, O. E., Goodman, R. M., Shelley, W. M., Bloodwell, R. D. Buerger's disease: A distinct clinical and pathologic entity. Journal of the American Medical Association 181(1): 5–12, July 7, 1962.

(57) Eisen, M. E. Coexistence of thromboangiitis obliterans and arteriosclerosis: Relationship to smoking. Journal of the American Geriatrics Society 14 (8): 846–858, August 1966.

(*153*) Razdan, A. N., Singh, R. P., Srivastava, V. K. Thromboangiitis obliterans. A clinical study of 125 cases. International Surgery; Bulletin 47(2): 122–125, February 1967.

(*32*) Brown, H., Sellwood, R. A., Harrison, C. V., Martin, P. Thromboangiitis obliterans. British Journal of Surgery 56 (1): 59–63, January 1969.

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Site of Action of Nicotine. The last sentence of the paragraph was not made by (181) Stromblad. As a matter of fact, Stromblad was not certain that nicotine caused the release of catecholamines and could not exclude a second mechanism. The 1971 document wants to protect the concept that nicotine primarily causes a release of catecholamines at the blood vessels.

Discussion

Nicotine has been thought to cause a peripheral vasoconstriction by way of the sympathetic nervous system. The present report shows that nicotine causes an immediate vasoconstriction in the human hand when injected into the brachial artery. This effect is likely to be due to a direct peripheral action of nicotine, especially as vasoconstrictor responses were absent from the contralateral hand.

According to the calculations of Boyle *et al.* (1947), based on the findings of Baumberger (1923), smoking of cigarettes with inhalation will give an absorption of nicotine equivalent to 2 mg. of nicotine bitartrate a minute. The flow in the brachial artery at the site used for infusion may be about one-hundreth of the cardiac output, and hence smoking would correspond to an infusion of some 20 μg./min. in this artery. In the present experiments this was just about the threshold dose for vasoconstriction in certain individuals. Moreover, it is quite possible that during prolonged smoking there may be an accumulation of nicotine in the blood, causing a higher dosage than calculated above. It is therefore likely that in some individuals the amount of nicotine absorbed during smoking is big enough to elicit a direct peripheral effect. These assumptions and calculations are not necessarily contradictory to earlier reports that sympathetic blockade abolishes the vascular effect of smoking, since there are great individual variations in sensitivity, and the early experiments with sympathetic blocking were made in only a few cases.

The mechanism of the peripheral action of nicotine is not known. However, the present observation that sympathicolytic agents prevent the vascular effect of nicotine is compatible with the assumption that nicotine acts by release of sympathicomimetic substances (for references see Burn and Randl, 1958). These substances may be released from the system of chromaffin cells lying close to the small vessels of the human skin (Adams-Ray and Nordenstam, 1956) or they could be released from the store which has been found in the arterial walls (Schmiterlow, 1948). A release from a chromaffin system would be consistent with the finding that ganglion-blocking agents prevent the effect of nicotine.

Another possible mechanism of the peripheral action of nicotine would be by excitation of a peripheral nervous plexus containing ganglion cells and adrenergic terminals. But so far no such peripheral nervous plexus has been definitely demonstrated (Folkow, 1956).

Summary

Nicotine was found to cause vasoconstriction in the hand when injected into the brachial artery. The threshold doses varied greatly between individuals, but, at least in some, the amount of nicotine assumed to be absorbed during smoking would be enough to cause vasoconstriction via a local mechanism. Sympathicolytics and ganglion-blocking agents abolished the effect of nicotine. This appears consistent with the assumption that nicotine causes a release of sympathicomimetics from the chromaffin system in the human skin, but could also be explained by the existence of a peripheral nervous plexus containing ganglion cells.

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CARDIOVASCULAR DISEASES

SUMMARY AND CONCLUSIONS

Coronary Heart Disease

1. Data from numerous prospective and retrospective studies confirm the judgment that cigarette smoking is a significant risk factor contributing to the development of coronary heart disease including fatal CHD and its most severe expression, sudden and unexpected death. The risk of CHD incurred by smokers of pipes and cigars is appreciably less than that by cigarette smokers.

2. Analysis of other factors associated with CHD (high serum cholesterol, high blood pressure, and physical inactivity) shows that cigarette smoking operates independently of these other factors and can act jointly with certain of them to increase the risk of CHD appreciably.

3. There is evidence that cigarette smoking may accelerate the pathophysiological changes of pre-existing coronary heart disease and therefore contributes to sudden death from CHD.

4. Autopsy studies suggest that cigarette smoking is associated with a significant increase in atherosclerosis of the aorta and coronary arteries.

5. The cessation of smoking is associated with a decreased risk of death from CHD.

6. Experimental studies in animals and humans suggest that cigarette smoking may contribute to the development of CHD and/or its manifestations by one or more of the following mechanisms:

a. Cigarette smoking, by contributing to the release of catecholamines, causes increased myocardial wall tension, contraction velocity, and heart rate, and thereby increases the work of the heart and the myocardial demand for oxygen and other nutrients.

b. Among individuals with coronary atherosclerosis, cigarette smoking appears to create an imbalance between the increased needs of the myocardium and an insufficient increase in coronary blood flow and oxygenation.

c. Carboxyhemoglobin, formed from the inhaled carbon monoxide, diminishes the availability of oxygen to the myocardium and may also contribute to the development of atherosclerosis.

d. The impairment of pulmonary function caused by cigarette smoking may contribute to arterial hypoxemia, thus reducing the amount of oxygen available to the myocardium.

e. Cigarette smoking may cause an increase in platelet adhesiveness which might contribute to acute thrombus formation.

Cerebrovascular Disease

1. Data from numerous prospective studies indicate that cigarette smoking is associated with increased mortality from cerebrovascular disease.

2. Experimental evidence concerning the relationship of smoking and cerebrovascular disease is at present insufficient to allow for conclusions concerning pathogenesis. However, some of the pathophysiological considerations discussed concerning CHD may also pertain to the relationship of smoking and CVD, particularly cerebral infarction.

Non-Syphilitic Aortic Aneurysm

Cigarette smoking has been observed to increase the risk of dying from nonsyphilitic aortic aneurysm.

Peripheral Vascular Disease

1. Data from a number of retrospective studies have indicated that cigarette smoking is a likely risk factor in the development of peripheral vascular disease. Cigarette smoking also appears to be a factor in the aggravation of peripheral vascular disease.

2. Cigarette smoking has been observed to alter peripheral blood flow and peripheral vascular resistance.

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Conclusion. After the appearance of the 1971 Document, Seltzer wrote a letter to the New England Journal of Medicine (288: 1186, 1973).

SMOKING AND CORONARY HEART DISEASE

To the Editor: In many, but not all, countries, cigarette smokers have been found to have higher rates of coronary heart disease than nonsmokers.[1] Even though dose-response relations and data on former cigarette smokers show a number of inconsistencies,[2,3] cigarettes have been accepted by the Public Health Service as "one of the major risk factors contributing to the development of . . . [coronary heart disease]."[4]

One of the particular strengths cited in governmental statements on cigarettes and lung cancer has been the interpretation of secular changes in lung-cancer mortality among British doctors, likening it to "that of a controlled cessation experiment."[4] As shown in Table 1,[5] mortality from this cause decreased by 25 per cent over a 12-year period in which the prevalence of cigarette smokers in the same population decreased by close to 50 per cent.

Table 1. Mortality from Lung Cancer and Coronary Heart Disease (CHD) among British Doctors 35 to 84 Years of Age.[5]

Prevalence of Cigarette Smokers		Age-Standardized Mortality (Rates/1000/Yr)		
yr	%	*period*	*lung cancer*	*CHD*
1951	41.3	1953-57	1.10	5.19
1957	32.9	1957-61	0.85	5.64
1966	21.3	1961-65	0.83	5.59
		% *change*		
		1st-2d period	−23	+9
		2d-3d period	− 2	−1
		1st-3d period	−25	+8

Now, if cigarette smoking were indeed clearly linked to coronary heart disease, by the same logic one would have expected to find a decrement in mortality from this cause over this period also. But inspection of these data (Table 1) reveals that, instead of decreasing, mortality actually increased by some 8 per cent.

Thus, the type of epidemiologic observations that provided the basis for the statement, "the reduction of rates experience in ex-smokers . . . is clearly shown in the case of lung cancer to be a reflection of significant change in risk,"[4] lends no support to the current enthusiasm for cigarette smoking as a major risk factor in coronary heart disease.

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(60) ENGLISH, J. P., WILLIUS, F. A., BERKSON, J. Tobacco and coronary disease. Journal of the American Medical Association 115(16): 1327–1329, October 19, 1940.

(131) MILLS, C. A., PORTER, M. M. Tobacco smoking and automobile-driving stress in relation to deaths from cardiac and vascular causes. American Journal of the Medical Sciences 234(1): 35–43, July 1957.

(33) BUECHLEY, R. W., DRAKE, R. M., BRESLOW, L. Relationship of amount of cigarette smoking to coronary heart disease mortality rates in men. Circulation 18(6): 1085–1090, December 1958.

TABLE A6.—*Coronary heart disease morbidity and mortality—retrospective studies*

(Actual number of cases shown in parentheses)[1]

[SM = Smokers NS = Nonsmokers EX = Ex-smokers]

Author, year, country, reference	Number and type of population	Data collection	Cases (percent)	Controls (percent)	Comments
English et al., 1940, U.S.A. (60).	1,000 males with manifest CHD, 40 years of age. Controls: 1,000 male non-CHD patients.	Case selection from Mayo Foundation files. Controls: same year of admission age-matched.	*Age* *Percent Smokers* 40–49 .....79.7 (187) 50–59 .....71.7 (392) 60 or over .....63.8 (431) All ages 69.8	*Percent Smokers* 61.9 (302) ($p<0.001$) 78.9 (371) (not significant) 61.8 (327) (not significant) 66.3 ($p<0.05$)	
Mills and Porter, 1957, U.S.A. (131).	474 white male coronary deaths. Controls: 605 white males.	Undefined.			
			40–49 *50–59* *60–69* *70 or over*	*40–49* *50–59* *60–69* *70 or over*	
			(66) (135) (153) (130)	(216) (188) (114) (88)	
			NS 7.14 6.66 19.30 33.84	19.91 24.47 35.09 64.12	
			All cigarettes 83.93 82.23 47.02 15.44	70.83 59.04 43.86 16.47	
			Pipes, cigars 8.93 11.11 32.63 47.70	9.26 16.47 21.05 29.41	
Buechley et al., 1958, U.S.A. (33).	Males reporting CHD to California Health Survey, with matched controls from same survey (included those surviving first myocardial infarction).	Questionnaire and interview.	NS .....20.4 (23) ≤20 .....61.1 (69) >20 .....18.6 (21)	NS .....42.1 (51) ≤20 .....46.3 (56) >20 .....11.6 (14)	

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TABLE A6.—*Coronary heart disease morbidity and mortality—retrospective studies (cont.)*

(Actual number of cases shown in parentheses)[1]

[SM = Smokers NS = Nonsmokers EX = Ex-smokers]

Author, year, country, reference	Number and type of population	Data collection	Cases (percent)	Controls (percent)	Comments
Russek and Zohman, 1958, U.S.A. (163).	97 male and 3 female coronary patients. Controls: 100 healthy controls of similar age, sex, occupation, and ethnic origin.	Interviews by authors.	*Tobacco usage>20 cigarettes/day* 70 percent.	35 percent.	Patients included 89 with classic myocardial infarction and 11 with angina pectoris.
Spain and Nathan, 1961, U.S.A. (176).	269 males identified as having CHD by physical examination and history. Controls: 2,637/3,000 males identified as not having CHD	3,000 males in New York City interviewed and examined by medical group.	NS .....39.0 (81) <40/day .....29.0 (78) >40/day .....13.0 (33) EX .....14.0 (38) Cigar, pipe .....14.0 (36) Total .....100.0(269)	29.0 (772) 53.0 (816) 9.0 (234) (p<0.05) 14.0 (361) 15.0 (400) 100.0(2,637)	
Mulcahy and Hickey, 1967 Ireland (135, 136).	403 men less than 60 years of age with classical CHD. Data compared with male population consumption figures.	Interview.	*Males* NS .....4.60 (18) SM .....89.75(362) EX .....4.75 (19) Total .....100.00(400)	*Males* 18.2(118) 76.6(427) 11.2 (68) 106.0(613)	Control smoking data obtained from estimated smoking habits of Irish population of same age group.
Schwartz et al., 1966, France (169).	612 male patients with angina or myocardial infarction. 612 age-matched controls.	Interview, laboratory, and clinical examinations.	Average amount per day as cigarettes .....18.6 All SM .....86.0 Inhalers 69.0	15.6 (p<0.0001) 86.0 46.0(p<0.00001)	Data apply only to those under 55 years of age.

TABLE A6.—*Coronary heart disease morbidity and mortality—retrospective studies (cont.)*

(Actual number of cases shown in parentheses)[1]

[SM = Smokers NS = Nonsmokers EX = Ex-smokers]

Author, year, country, reference	Number and type of population	Data collection	Cases (percent)			Controls (percent)		Comments
			Males (72)	*Females* (21)	*Males* (72)	*Females* (84)		
Viliger and Heyden-Stucky, 1966, Switzerland (201).	103 cases with recent myocardial infarctions. 72 males, 25 females, 100 age-matched controls (72 male industrial employees and 28 females in hospital for other diagnoses).	Hospital history or interview.	NS 4.94	32.4	†21.9	32.1		These are not pure smoking classes. †(p<0.01)
			Cigarette 66.7	28.6	48.6	14.3		
			1–19 cigarettes/day 18.1	10.7	23.6	10.7		
			>20 .....48.6	17.9	†22.2	3.6		
			Cigar, pipe 44.4	...	27.5	..		
			EX 4.2	...	†18.5	3.6		
Dörken, 1967, Germany (52).	385 males up to 44 years of age with myocardial infarction or sudden death (133 deceased, 66 living). Controls—Hamburg age-matched citizens selected randomly.	Death certificate review. Interview of patient or kin.	NS .....1.9 (2) *Cigarette Units* 1–5 .....1.2 (3) 10–15 .....32.3 (62) 20–30 .....43.6 (84) >35 .....21.2 (42) 100.0(193) (only 28 were mixed or cigar smokers)			18.4 (74) 16.0 (43) 60.8(192) 22.6 (92) 2.2 (9) 100.0(413) (62 were mixed or cigar smokers)		Ex-smokers listed under nonsmokers. Smoking information available only on 193/385. Three cigarette categories include mixed or cigar smokers recalculated as to number of cigarettes. No patients or controls smoked pipes exclusively.
Dörken, 1967, Germany (53).	83 females up to 44 years of age with myocardial infarction or sudden death. Controls—125 females 21–44 years of age from clinic without CVD or lung cancer.	Death certificates, interviews.	*Cigarettes per day* 0 .....6.1 (8) 1–5 ..... 6–15 .....48.6 (16) 20–30 .....30.4 (18) >35 .....6.1 (2)			63.2(84) (p<0.001) 17.3(23) 16.5(22) 3.0 (4) ...		

(163) RUSSEK, H. I., ZOHMAN, B. L. Relative significance of heredity, diet and occupational stress in coronary heart disease of young adults. Based on an analysis of 100 patients between the ages of 25 and 40 years and a similar group of 100 normal control subjects. American Journal of the Medical Sciences 235(3): 266–277, March 1958.

(176) SPAIN, D. M., NATHAN, D. J. Smoking habits and coronary atherosclerotic heart disease. Journal of the American Medical Association 177 (10): 637–683, September 9, 1961.

(135) MULCAHY, R., HICKEY, N. J. Cigarette smoking habits of patients with coronary heart disease. British Heart Journal 28: 401–408, 1966.

(136) MULCAHY, R., HICKEY, N. J. The role of cigarette smoking in the causation of atherosclerosis. Geriatrics 22(2): 165–174, February 1967.

(169) SCHWARTZ, D., LELLOUCH, J., ANGUERA, G., BEAUMONT, J. L., LENEGRE, J. Tobacco and other factors in the etiology of ischemic heart disease in man: Results of a retrospective survey. Journal of Chronic Diseases 19(1): 35–55, January 1966.

(201) VILIGER, U., HEYDEN-STUCKY, S. Das Infarktprofil. Unterschiede zwischen infarktpatienten und Kontrollpersonen in der Ostschweiz. (The infarct profile. Differences between infarct patients and controls in East Switzerland.) Schweizerische Medizinische Wochenschrift 96(23): 748–758, June 11, 1966.

(52) DÖRKEN, H. Die Rauchgewohnheitenbei jüngeren Herzinfarkt-Patienten. (Smoking habits of younger patients with myocardial infarction.) Munchener medizinische Wochenschrift 109(4): 187–192 January 27, 1967.

(53) DÖRKEN, H. Die Rauchgewohnheiten bei jüngeren Frauen mit Herzinfarkt. (The smoking habits of younger females with myocardial infarction.) Munchener medizinische Wochenschrift 109(41): 2129 2134, October 13, 1967.

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TABLE A6.—*Coronary heart disease morbidity and mortality—retrospective studies (cont.)*

(Actual number of cases shown in parentheses)[1]

[SM = Smokers NS = Nonsmokers EX = Ex-smokers]

Author, year, country, reference	Number and type of population	Data collection	Cases (percent)	Controls (percent)	Comments
Hyams et al., 1967, Japan (87).	73 males surviving myocardial infarction. 157 age-matched controls hospitalized for non-CVD but include hypertensive disease.	Interviews by trained personnel.	NS .....10.1 (8) 1-9 cigarettes per day ..... 7.0 (5) 10-15 .....25.4 (18) 16-20 .....35.2 (25) 21-24 .....22.5 (16) >25 ..... 9.9 (7) All SM 100.0 (71)	21.0 (33) 10.6 (15) 23.0 (42) 25.8 (32) 17.7 (22) 12.1 (16) 100.0(124)	
Mulcahy et al., 1967, Ireland (137).	100 female patients less than 60 years of age admitted to hospital with CHD.	Hospital interviews.	SM .....63.0 (63) NS .....33.0 (33) EX ..... 4.0 (4) Total .....100.0(100)	45.6(281) 45.3(259) 9.1 (62) 100.0(572)	Smoking on controls obtained from statistics of smoking in Irish Republic. Sudden death not included.
Stejfa, 1967, Poland (179).	70 male and female patients with recent onset exertional angina pectoris. 54 controls of same age.	Direct interviews.	*Prevalence of risk factors* *Angina patients* 60.0	*Control group* 48.1(p>0.1)	Authors then followed the 70 patients for 3 years and noted that smoking significantly influenced the incidence of coronary occlusion.
Schimmler et al., 1968, Germany (167).	503 males with healed myocardial infarctions. 714 male controls of same age without detectable heart disease.	Hospital interviews.	NS ..... 9.0 (44) EX .....12.0 (59) Cigar, pipe ..... 12.0 (62) <19 cigarettes ....25.0(129) >20 .....42.0(209) Total .....100.0(503)	26.0(167) (p<0.001) 20.0(142) (p<0.001) 11.0 (77) 16.0(101) (p<0.001) 29.0(207) (p<0.001) 100.0(714)	

TABLE A6.—*Coronary heart disease morbidity and mortality—retrospective studies (cont.)*

(Actual number of cases shown in parentheses)[1]

[SM = Smokers NS = Nonsmokers EX = Ex-smokers]

Author, year, country, reference	Number and type of population	Data collection	Cases (percent)	Controls (percent)	Comments
Hood et al., 1969, Sweden (85).	230 males surviving early first myocardial infarction. Controls: 855 randomly selected males 50 years of age.	Interview and examination.	(230) Never smoked ....1.75 EX before infarction .....1.75 EX after infarction .....29.1 <15 cigarettes ...28.3 >15 cigarettes ...22.6 AB .....80.0 Pipe 16.5	(855) 24.3 10.7 -- 27.4 26.0 47.4 8.8	
Jouve et al., 1969, France (91).	1,229 CHD patients; 802 males, 427 females. Controls: 743 individuals of both sexes: age, sex, and social class matched.	Interview.	43.0	33.0(p<0.0001)	
Kastl, 1969, Germany (98).	273 male railway employees up to 65 years of age surviving myocardial infarction. 275 control employees with minor circulatory disturbances.	Interview and examination.	NS .....20.0 (55) 2-20 cigarettes or up to 6 cigars. ..32.0 (88) >20 cigarettes or >6 cigars. .....48.0(132)	29.8 (82) 63.3 (83) 6.8 (19)	

[1] Unless otherwise specified, disparities between the total number of cases and the sum of the individual smoking categories are due to the exclusion of either occasional, miscellaneous, mixed, or ex-smokers.

(87) HYAMS, L., SEGI, M., ARCHER, M. Myocardial infarction in the Japanese. A retrospective study. American Journal of Cardiology 20(4): 549–551, October 1967.

(137) MULCAHY, R., HICKEY, N. J., MAURER, B. J. Coronary heart disease in women. Study of risk factors in 100 patients less than 60 years of age. Circulation 36(4): 577–586, October 1967.

(179) STEJFA, M., JR. Predictive significance of risk factors in exertional angina pectoris. Cardiologia 51(6): 336–339, 1967.

(167) SCHIMMLER, W., NEFF, C., SCHIMERT, G. Risikofaktoren und Herzinfarkt. Eine retrospektive studie. (Risk factors and myocardial infarct. A retrospective study.) Münchener Medizinische Wochenschrift 110(27): 1585–1594, July 5, 1968.

(85) HOOD, B., TIEBLIN, G., WELIN, G., ORNDAHL, G., KORSAN-BENGTSEN, K. Myocardial infarction in early age. III. Coronary risk factors and their deficient control. Acta Medica Scandinavica 185(4): 241–251, April 1969.

(91) JOUVE, A., ROCHU, P., AVRIL, P. Enquetes epidemiologiques sur l'atherosclerose dans la region Provencale. (Epidemiological investigations of atherosclerosis in the Provence region.) Union Médicale du Canada 98(5): 761–766, May 1969.

(98) KASTL, O. Berufliche und Umweltanalyse infarktkranker Eisenbahnbediensteter. (Occupational and environmental analysis of infarct patients in railway service.) Medizinische Klinik 64(42): 1911-1917, October 17, 1969.

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TABLE A7.—*Differences in serum lipids between smokers and nonsmokers (cont.)*

(Actual number of individuals shown in parentheses)[1]

[SM = Smokers NS = Nonsmokers]

Author, year, country, reference	Number and type of population	Results	Comments
Acheson and Jessop, 1961 Ireland (1).	221 randomly chosen pensioners 65–85 years of age.	*Mean serum cholesterol mg. percent* / *Mean Beta/Alpha lipoprotein ratio* NS ..... 214(33) / 2.0(36) 5 cigarettes/day ..... 201(12) / 2.1(11) 10 ..... 213(34) / 1.9(33) 20 ..... 221(33) / 1.9(25) >30 ..... 206 (8) / 1.8 (8)	
Bronte-Stewart, 1961, South Africa (31).	Approximately 600 healthy males 25–55 years of age.	*Cholesterol mg. percent* / *Beta/Alpha lipoprotein ratio* 25–39: †A ‡E — 40–55: A E — 25–39: A E — 40–55: A E NS ..... 179 197 222 245 3.83 3.84 3.75 4.69 "Heavy" SM .. 156 223 204 256 3.82 4.40 4.07 5.40	No data given on numbers in each group. †A—African. ‡E—European.
Konttinen, 1962, Finland (119).	314 male military recruits 18–25 years of age.	*Serum cholesterol mg. percent* / *Serum phospholipide mg. percent* NS .....(145)..... 203.8 / 218.0 (Cigarettes per day) 1–10 (53)..... 206.8 / 222.3 11–19 .....(64)..... 215.1 / 224.7 >20 .....(62)..... 202.3 / 210.5	No serum lipid differences found among the various smoking groups.
Blomstrand and Lundman, 1966, Sweden (26).	76 monozygotic twin pairs and 87 dizygotic twin pairs obtained from Swedish Twin Registry.	I. Monozygotes discordant for smoking: Smokers showed slightly lower levels of cholesterol, triglycerides, and phospholipids than nonsmokers. II. Dizygotes discordant for smoking: Smokers showed significantly higher levels of phospholipids. No differences for cholesterol and triglycerides.	The authors conclude from the differing MZ and DZ results that constitutional factors are probably more important than smoking in determining lipid levels.

TABLE A7.—*Differences in serum lipids between smokers and nonsmokers*

(Actual number of individuals shown in parentheses)[1]

[SM = Smokers NS = Nonsmokers]

Author, year, country, reference	Number and type of population	Results	Comments
Gofman et al., 1955, U.S.A., (72).	401 male employees 20–59 years of age.	*Difference between SM and NS* Lipid: / *Ages 20–29* (NS 66, SM 37) / *Ages 30–39* (NS 56, SM 67) / *Ages40–59* (NS 17, SM 44) ‡Sf 0–12 ..... +59.9 p<0.001 / +19.9 p<0.05 / + 3.9 p<0.05 Sf 12–20 ..... + 9.4 p<0.001 / + 5.4 p<0.05 / − 3.6 p<0.05 Sf 20–100 ..... +20.0 p<0.025 / + 9.1 p<0.05 / + 8.5 p<0.05 Sf 100–400 ..... +15.8 p<0.025 / +12.1 p<0.05 / − 4.5 p<0.05 Cholesterol ..... +21.2 p<0.05 / + 9.0 p<0.05 / − 4.8 p<0.05	‡Sf refers to Svedberg flotation units of centrifuged lipoproteins.
Thomas, 1958, U.S.A. (185).	621 medical students.	*Serum cholesterol mg. percent* *NS (364)* Observed/Expected / *SM (257)* Observed/Expected <250 ..... 170/157 / 149/161.6 >250 ..... 87/99.6 / 116/102.4 Chi Square Value = 8.2 p<0.025	
Dawber et al., 1959, U.S.A. (47).	2,253 males participating in the Framingham study 29–59 years of age.	*Serum cholesterol mg. percent* *30–44* / *45–59* NS ..... 216.1(149) / 228.3(131) All cigarettes ..... 224.8(674) / 229.5(589) <10 ..... 217.4 (76) / 229.1 (76) 10–19 ..... 221.1(134) / 230.1 (96) 20–39 ..... 225.8(551) / 227.8(350) >40 ..... 229.0(114) / 238.5 (68) Pipe and cigar ..... 214.9(128) / 227.1(116)	The authors conclude that there is evidence of a gradient of cholesterol with increasing amount of cigarette smoking in younger men.
Karvonen et al., 1959, Finland (97).	525 males in various occupations 20–59 years of age.	*Serum cholesterol mg. percent* *West Finland* / *East Finland* / *Helsinki* NS ..... 205.0(64) 226.6 (39) 235.1 (62) SM ..... 228.7(91) 249.7(103) 257.8(166)	The authors state that no trend was noted associating increasing amount smoked with increasing serum cholesterol, although smokers and nonsmokers did have different overall means.

(72) GOFMAN, J. W., LINDGREN, F. T., STRISOWER, B., DELALLA, O., GLAZIER, F. TAMPLIN, A. Cigarette smoking, serum lipoproteins, and coronary heart disease. Geriatrics 10(8); 349–354, August 1955.

(185) THOMAS, C. B. Familial and epidemiologic aspects of coronary disease and hypertension. Journal of Chronic Diseases 7(3): 193–208, March 1958.

(47) DAWBER, T. R., KANNEL, W. B., REVOTSKIE, N., STOKES, J., KAGAN, A., GORDON, T. Some factors associated with the development of coronary heart disease. Six years' followup experience in the Framingham study. American Journal of Public Health and the Nation's Health 49(10): 1349–1356, October 1959.

(97) KARVONEN, M., ORMA, E., KEYS, A., FIDANZA, F. BROZEK, J. Cigarette smoking, serum-cholesterol, blood-pressure, and body fatness. Observations in Finland. Lancet 1: 492–494, March 7, 1959.

(1) ACHESON, R. M., JESSOP, W. J. E. Tobacco smoking and serum lipids in old men. British Medical Journal 2: 1108–1111, October 28, 1961.

(31) BRONTE-STEWART, B. Cigarette smoking and ischaemic heart disease. British Medical Journal 1: 379–384, February 11, 1961.

(119) KONTTINEN, A. Cigarette smoking and serum lipids in young men. British Medical Journal 1: 1115–1116, April 21, 1962.

(26) BLOMSTRAND, R., LUNDMAN, T. Serum lipids, smoking and heredity. Acta Medica Scandinavica 180(Supplement 455): 51–60, 1966.

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TABLE A7.—*Differences in serum lipids between smokers and nonsmokers (cont.)*

(Actual number of individuals shown in parentheses)[a]

[SM = Smokers NS = Nonsmokers]

Author, year, country, reference	Number and type of population	Results	Comments
Higgins and Kjelsberg, 1967, U.S.A. (83).	5,030 male and female residents of Tecumseh, Michigan, 16–79 years of age.	*Males* / *Females* NS ..... 209.9 (360) / 210.1 (1,439) Cigarette ..... 212.5 (1,426) / 212.4 (910)	
Pincherly and Wright, 1967, England (150).	2,000 men participating in executive health examinations 28–70 years of age.	*Serum cholesterol mg. percent* / *Percentage with serum cholesterol >270 mg. percent* NS (677) ..... 236.2 / 19.0 Ex-smoker (388) ..... 246.0 / 28.0 1–19 cigarettes/day (424) ..... 239.2 / 24.0 >20 cigarettes/day (611) ..... 249.4 / 30.0	The authors noted that smokers showed significantly higher ($p<0.001$) serum cholesterol levels than nonsmokers.
Van Buchem, 1967, Netherlands (199).	918 randomly chosen males 40–59 years of age for entry into prospective study.	*Serum cholesterol* *0–209 mg. percent* / *210–249 mg. percent* / *>250 mg. percent* NS ..... 12.4 (32) / 14.0 (44) / 14.2 (41) Cigarette SM ..... 71.6 (184) / 67.8 (213) / 68.2 (197) Other ..... 16.0 (41) / 18.2 (57) / 17.6 (51)	The authors found no correlation between smoking and serum cholesterol levels.
Boyle et al., 1968, U.S.A. (28).	1,104 male factory employees 20–64 years of age.	*Serum cholesterol mg. percent* / *Serum Beta-lipoprotein mg. percent* NS ..... 243 (519) / 0.325 } $p<0.005$ / $p<0.001$ SM ..... 251 (576) / 0.352 }	Beta-lipoproteins were found to increase with age, but smokers had higher levels than nonsmokers at all ages.
Caganova et al., 1968, Czechoslovakia (56).	49 males living in youth hostel, 21.6 average age.	*Serum cholesterol mg. percent* / *Serum Beta-lipoprotein mg. percent* NS (34) ..... 188.20 } $p<0.025$ / 359.80 } $p<0.001$ SM (15) ..... 214.20 } / 458.40 } *Beta/alpha lipoprotein ratio* NS (34) ..... 1.16 } $p<0.025$ SM (15) ..... 1.85 }	

TABLE A7.—*Differences in serum lipids between smokers and nonsmokers (cont.)*

(Actual number of individuals shown in parentheses)[a]

[SM = Smokers NS = Nonsmokers]

Author, year, country, reference	Number and type of population	Results	Comments
Fidanza et al., 1966, Italy (62).	111 male prisoners 34–69 years of age.	*Serum cholesterol mg. percent* *Ages <19* / *20–29* / *30–39* / *40–49* NS .... / 195 (12) / 189 (10) / 176 (7) <20 cigarettes/day ..... 208 (5) / 201 (16) / 202 (13) / 195 (10) >20 cigarettes/day ..... 197 (6) / 175 (7) / 171 (7) / .. *Serum triglycerides mg. percent* NS .... / 84.7 / 71.9 / 85.0 <20 cigarettes/day ..... 84.5 / 92.4 / 101.9 / 89.8 >20 cigarettes/day ..... 91.0 / 86.0 / 65.7 / ..	No statistically significant differences found between SM and NS.
Kedra and Dmowski, 1966, Poland (99).	200 clinically healthy males 20–50 years of age.	*Serum cholesterol mg. percent* / *Phospholipids mg. percent* / *Total lipids mg. percent* NS (100) ..... 210.2 } $p<0.01$ / 255.1 } $p>0.05$ / 1,234.8 } $p<0.01$ SM 100) ..... 224.9 } / 257.5 } / 1,362.1 } *Total fatty acids mg. percent* / *Beta-lipoproteins percent of total lipoproteins* NS (100) ..... 797.8 } $p<0.01$ / 43.1 } $p<0.01$ SM 100) ..... 869.9 } / 49.9 }	Serum cholesterol also noted to increase with increasing intensity and duration of smoking.
Harlan et al., 1967, U.S.A. (79).	667 former naval aviation cadets 48 years of age (average).	*Serum cholesterol*: Found to be related to cigarette smoking $p<0.05$. *Serum triglycerides*: Found not to be related to cigarette smoking. *Lipoproteins*: Sf 0–12 related. $p<0.05$ Sf 20–100 unrelated. Sf 100–400 unrelated.	
Heyden-Stucky and Schibler-Reich, 1967, Switzerland (82).	600 plant workers 30–60 years of age.	*Serum cholesterol mg. percent* / *Serum triglycerides mg. percent* <10 cigarettes/day ..... 210.0 (334) / 110.0 >10 cigarettes/day ..... 260.0 (166) / 180.0	No statistically significant difference found between SM and NS.

(62) FIDANZA, F., IMBIMBO, B., DI BENEDETTA, C. Indagine epidemiologica delle cardiopatie ischemiche nei reclusi del penitenziario di S. Stefano di Ventotene. (Epidemiological investigation of ischemic heart disease in prisoners of S. Stefano di Ventotene prison.) Giornale dell' Arteriosclerosi 4: 255–267 1966.

(99) KEDRA, M., DMOWSKI, G. The influence of tobacco smoking on the development of atherosclerosis and on the composition of blood lipids. Polish Medical Journal 5(1): 37–43, 1966.

(79) HARLAN, W. R., OBERMAN, A., MITCHELL, R. E., GRAYDIEL, A. Constitutional and environmental factors related to serum lipid and lipoprotein levels. Annals of Internal Medicine 66(3): 540–555, March 1967.

(82) HEYDEN-STUCKY, S., SCHIBLER-REICH, S. Kardiologische Risikofaktoren bei Schweizer Mannern. (Cardiological risk factors in Swiss men.) Schweizerische Medizinische Wochenschrift 97(1): 20–25, January 7, 1967.

(83) HIGGINS, M. W., KJELSBERG, M. Characteristics of smokers and nonsmokers in Tecumseh, Michigan. II. The distribution of selected physical measurements and physiologic variables and the prevalence of certain diseases in smokers and nonsmokers. American Journal of Epidemiology 86(1): 60–77, July 1967.

(150) PINCHERLE, G., WRIGHT, H. B. Screening in the early diagnosis and prevention of cardiovascular disease. Journal of the College of General Practitioners 13: 280–289, 1967.

(199) VAN BUCHEM, F. S. P. Serum lipids, nutrition and atherosclerotic complications in man. Acta Medica Scandinavica 181(4): 403–416, April 1967.

(28) BOYLE, E., JR., MORALES, I. B., NICHAMAN, M. Z., TALBERT, C. R., JR., WATKINS, R. S. Serum beta lipoproteins and cholesterol in adult men. Relationships to smoking, age, and body weight. Geriatrics 23(12): 102–111, December 1968.

(56) CAGANOVA, A., CAGAN, S., SIMKO, V. Lipidy krvneho sera u nefajciarov a fajciarov. (Blood serum lipids in nonsmokers and smokers.) Bratislavske Lekarske Listy 50(3): 387–392, September 3, 1968.

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TABLE A7.—*Differences in serum lipids between smokers and nonsmokers (cont.)*

(Actual number of individuals shown in parentheses)[a]

[SM = Smokers NS = Nonsmokers]

Author, year, country, reference	Number and type of population	Results			Comments
Modzielewski and Malec, 1969, Poland (*133*).	140 males 20–68 years of age.	*Serum cholesterol* NS (20) p<0.01 Heavy smokers	*Serum Beta-lipoproteins* NS p<0.01 Heavy smokers	*Serum free fatty acids* NS p<0.01 Heavy smokers	
Kjeldsen, 1969, Denmark (*115*).	934 employees of various firms in Copenhagen.		*Serum cholesterol mg. percent*		
		NS (196)	236	p<0.01	
		SM (735)	241		
Pozner and Billimoria, 1970, England (*151*).	64 male and female healthy volunteers 19–30 years of age.		*Serum cholesterol mg. percent*	*Serum triglycerides mg. percent* / *Total phospholipids mg. percent*	Significant figures refer to heavy smokers as compared with nonsmokers.
		NS(20)	176.3	68.6 / 193.4	
		Light SM(17) (Over 7.3 cigarettes/day)	172.1	68.4 / 188.9	
		Heavy SM(27) (Over 22.8 cigarettes/day)	200.0 p<0.05	87.6 p>0.05 / 218.6 p<0.001	

[a] Unless otherwise specified, disparities between the total number of cases and the sum of the individual smoking categories are due to the exclusion of either occasional, miscellaneous, mixed, or ex-smokers.

(*133*) MODZELEWSKI, A., MALEC, A. Zachowanie sie niektorych lipidow we krwi u palaczy. (Patterns of certain blood lipids in smokers.) Wiadomosci Lekarskie 22(3): 229–233, February 1, 1969.

(*151*) POZNER, H., BILLIMORIA, J. D. Effect of smoking on blood-clotting and lipid and lipoprotein levels. Lancet 1(7660): 1318–1321, June 20, 1970.

(*56*) EDWARDS, F., MCKEOWN, T., WHITFIELD, A. G. W. Association between smoking and disease in men over sixty. Lancet 1: 196–200, January 24, 1959.

(*43*) CLARK, V. A., CHAPMAN, J. M., COULSON, A. H. Effects of various factors on systolic and diastolic blood pressure in the Los Angeles Heart Study. Journal of Chronic Diseases 20: 571–581, 1967.

TABLE A8.—*Blood pressure differences between smokers and nonsmokers*

(Actual number of individuals shown in parentheses)[a]

[SM = Smokers NS = Nonsmokers]

Author, year, country, reference	Number and type of population	Results				Comments
Dawber et al., 1959, U.S.A. (*47*).	1,253 male and female residents of Framingham.			*Systolic blood pressure*		No association found between systolic blood pressure and smoking.
				Ages 38–44	*45–59*	
		NS(149)		138.8	143.0	
		Cigarettes(574)		132.5	140.3	
		<10(75)		134.7	144.0	
		10–19(154)		129.4	141.6	
		20–39(551)		132.2	138.9	
		>40(114)		136.1	141.5	
		Pipe and cigar(128)		135.0	141.9	
Edwards et al., 1959, England (*56*).	1,737 male patients of general practitioners over 60 years of age.			*Proportion of males with "Hypertension" (≥200/≧100 mm. Hg.)*		
		NS		27.2 percent (151)		
		Cigarettes		20.5 percent (720)		
		Pipe		25.9 percent (341)		
Karvonen et al., 1959, Finland (*97*).	525 males in various regions of Finland 20–69 years of age.		*West Finland*	*Systolic blood pressure* *East Finland*	*Helsinki*	No data on pipe and cigar smokers. No statistical significance noted.
		NS	139.2(64)	142.6 (39)	132.8 (62)	
		SM	138.3(91)	135.4(103)	129.8(166)	
				Diastolic blood pressure		
		NS	84.7	86.8	89.6	
		SM	81.9	84.1	86.8	
Clark et al., 1967, U.S.A. (*43*).	1,859 male civil servants.		*Mean systolic blood-pressure*		*Mean diastolic blood-pressure*	Nonsmoker and smoker groups were of similar average age.
		NS(728)	137.0		83.9	
		SM(607)	133.6	(p≤0.05)	82.6	(p≤0.05)

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Serum Lipid Differences. The tabulated material of (151) Pozner and Billimoria was subsequently challenged by Howell in a letter to the Editor (Br Med J 22 April 1972).

Smoking and Vascular Disease

SIR,—Your leading article (1 April, p. 3) states unequivocally, "The medical profession is the only professional group in which cigarette smoking has lessened," without the support of any references. I would doubt if each and every professional group has been adequately sampled and reported on. *Smoking and Health Now*[1] reports that after the publication of the 1962 report there was a sharp reduction in the number of men smoking cigarettes, a reduction maintained in social classes I, II, and III. The professional groups fall in these classes.

Your article goes on to point out that Pozner and Billimoria[2] (in a small selected sample) found that "fasting plasma turbidity, cholesterol, and β and pre-β lipoproteins were significantly increased in heavy smokers," but you failed to make the most important point that in male heavy smokers only pre-β lipoprotein means were significantly higher than those of non-smokers. In a sample of 2,433 middle-aged males Howell[3] failed to find significant correlation between smoking and haemoglobin, E.S.R., serum cholesterol, β lipoprotein, and uric acid levels. The one striking finding—namely, a significantly increased white blood cell count in heavy smokers—has now been confirmed by Corre, Lellouch, and Schwartz.[4] In some small way this may provide confirmation that the sample used by Howell was not atypical for males of that age group with an average smoking history extending over 20 years.—I am, etc.,

R. W. HOWELL

Tilehurst, Berks

1 Royal College of Physicians, *Smoking and Health Now*. London, Pitman, 1971.
2 Pozner, H., and Billimoria, J. D., *Lancet*, 1970, 1, 1313.
3 Howell, R. W., *Lancet*, 1970, 2, 152.
4 Corre, F., Lellouch, J., and Schwartz, D., *Lancet*, 1971, 2, 632.

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Hypertension in Nonsmokers. The articles which do not show the health hazards of smoking are inserted in these tables. This is unfortunate, because the significance of the observations are lost and buried underneath the selected papers. The Results of (56) Edwards are as follows:

Hypertension

In view of the continuous distribution of arterial pressure, a full assessment of the effect of smoking requires a more critical appraisal than we can attempt here. Nevertheless the limited data available for the preliminary note suggested that, even when men are identified arbitrarily as hypertensive (that is with systolic or diastolic pressures above 200 or 100 mm. Hg respectively), a relationship to smoking was apparent. It was therefore thought worth while to use the data now available for all men over 60 for a more complete examination of this relationship.

TABLE XI—PROPORTION (%) OF MEN WITH HYPERTENSION ACCORDING TO SMOKING HABITS AND AGE

Age (yr.)	Men not smoking	Men smoking		All men who have never smoked cigarettes
		Cigarettes	Pipe	
60–64	14·9	14·9	13·9	16·3
65–69	21·4	12·2	17·6	20·2
70–74	40·4	34·7	31·3	35·5
75 and over	36·5	32·0	34·7	35·1
Total	29·2	20·5	25·9	27·2

TABLE XII—PROPORTION (%) OF MEN WITH HYPERTENSION ACCORDING TO SMOKING HABITS AND SOCIAL CLASS

Social class	Men not smoking	Men smoking		All men who have never smoked cigarettes
		Cigarettes	Pipe	
I & II	24·5	18·9	20·3	21·6
III	31·1	19·8	28·0	30·2
IV & V	24·1	23·1	26·1	24·8

Table XI gives the percentages of men with pressures above the limits referred to according to age and smoking habits. As would be expected, the percentages are much higher above than below 70, although they do not appear to differ appreciably in the age-groups 70–74 and 75 and over. But at all ages the incidence of hypertension is lower in cigarette-smokers than in men not smoking. The frequency in pipe-smokers is intermediate between that of the two previous groups, but is much nearer to the level in cigarette-smokers than in men not smoking. In this case, therefore, unlike the two previously considered, the effect on arterial pressure seems to be common to cigarette- and pipe-smokers.

The relationship between the incidence of hypertension and social class (table XII) is not regular. High pressures are, however, less common in cigarette-smokers than in men not smoking.

Discussion

Some of the criticisms of the evidence relating smoking to disease are overcome by investigation of a random sample of the general population. By this method it is possible to examine the frequency of disease in smokers and non-smokers—a procedure less open to criticism than a comparison of the smoking habits of the affected individuals with those of a control group. Already some fairly large populations have been assembled in which the incidence of mortality from specific diseases has been related to smoking. But data in respect of morbidity are also required, and the populations which can be studied are inevitably much smaller. In practice investigation of the effects of smoking on morbidity in a sample of the general population is almost inevitably restricted to the common diseases.

In the present assessment of the effects of smoking in 1737 representative men over the age of 60, we have considered only the eight most common diseases or disabilities. Three diseases—bronchitis, peptic ulcer, and hypertension—were consistently related to smoking habits. Bronchitis and peptic ulcer were commoner in men smoking than in men not smoking and increased in frequency with increasing amounts smoked. The incidence of both diseases was higher in poorly paid (classes IV and V) than in well-paid occupations (classes I and II). The relationship of smoking to incidence, however, appeared to be independent of social class. (Expressed differently, in all classes the frequency of the diseases was increased by smoking.) In general the experience of pipe-smokers was about the same as that of men not smoking, the increased risks being apparently restricted to cigarette-smokers. The observations on bronchitis are consistent with previous reports (Oswald and Medvei 1955, Ogilvie and Newell 1957), and those on peptic ulcer confirm and extend results described by Doll et al. (1958).

The frequency of hypertension (arterial pressures above 200 mm. Hg systolic or 100 mm. Hg diastolic) was greater in men not smoking than in cigarette- or pipe-smokers, and in this case incidence was inversely related to amounts smoked. This finding was observed in each of the occupational groups considered, but there was no consistent relationship between incidence and social class. Pressures in men who had given up smoking were approximately the same as in those who had never smoked. These results suggest that the lowering of arterial pressure produced by smoking is a short-term one and disappears after smoking is stopped for a period.

For reasons referred to earlier, in interpretation of the effects of smoking the common conditions whose incidence was not associated with it—coronary-artery disease, arthritis, defective hearing, and defective vision—are almost as significant as those which are. It must be remembered, of course, that observations on living men are incomplete; for example, there is a good deal of evidence that mortality due to coronary-artery disease is related to smoking (Hammond and Horn 1954, Doll and Hill 1956). Nevertheless the facts that the common diseases with which smoking is so consistently associated are those in which an oral or respiratory irritant might be expected to be significant, and in which smoking had been mentioned as an aetiological influence long before there was direct evidence, meet to some extent the reservation that smokers as a class may be genetically more susceptible to the diseases associated with smoking.

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TABLE A3.—*Blood pressure differences between smokers and nonsmokers (cont.)*

(Actual number of individuals shown in parentheses)[1]

[SM = Smokers NS = Nonsmokers]

Author, year, country, reference	Number and type of population	Results					Comments
Higgins and Kjelsburg, 1967, U.S.A. (83).	5,030 male and female residents of Tecumseh, Michigan, 16–79 years of age.		*Age adjusted mean systolic blood pressure*		*Age adjusted mean diastolic blood pressure*		
			Males	*Females*	*Males*	*Females*	
		NS	127.9 (360)	84.5 (1419)	136.6 (360)	82.1 (1420)	(p<0.001)
		Cigarette	136.4 (1426)	81.4 (910)	131.8 (1426)	79.0 (910)	
Reid et al., 1967, England (155).	676 male British and 625 male American postal workers 40–59 years of age.		*Mean systolic blood pressure (adjusted for difference in weight)*		*Mean diastolic blood pressure*		The author did note SM-NS blood pressure differences prior to controlling for weight, but not after such control.
			UK	*U.S.A.*	*UK*	*U.S.A.*	
		NS	128.2 (45)	126.8 (99)	78.5	81.0	
		1–14 grams	130.2 (27)	133.0 (60)	79.4	82.1	
		15–24 grams	128.5 (232)	127.7 (169)	78.6	77.8	
		>25 grams	127.9 (70)	128.1 (218)	77.5	77.1	
		All amounts	129.1 (519)	128.6 (417)	78.7	77.8	
Tibblin, 1967, Sweden (157).	895 males in Göteborg, Sweden, born in 1913.		*Blood pressure* ≦110/≦70 (88)	*115–115/ 75–95 (463)*	*130–170/ 100–110 (220)*	>175/>115 (78)	Numbers in parentheses represent total in blood pressure group. The author noted a stepwise decrease with level of blood pressure as smoking increased.
		NS	18.0	25.0	25.5	34.7	
		1–14 cigarettes	29.2	29.2	25.5	18.7	
		>15 cigarettes	28.1	30.9	18.5	17.3	
		Pipe and cigar	11.2	5.6	10.0	4.0	

[1] Unless otherwise specified, disparities between the total number of individuals and the sum of the individual smoking categories are due to the exclusion of either occasional, miscellaneous, mixed, or ex-smokers.

(157) TIBBLIN, G. High blood pressure in men aged 50. A population study of men born in 1913. Acta Medica Scandinavica (Supplementum 470): 1–84, 1967.

TABLE A17.—*Incidence of new coronary heart disease by smoking category and behavior type for men 39–49 years of age*

(Numbers in parentheses are number of CHD cases in each subgroup)

Behavior type	Smoking group						
	Never smoked	Former cigarette smokers	Current and former pipe and cigar only	Cigarettes			Total
				1–15	16–25	26 and over	
A	16.3(5)	13.8 (7)	1.3(1)	1.6(1)	15.8(15)	14.9(16)	9.3(45)
B	1.3(2)	5.1 (3)	2.2(2)	7.3(4)	3.1 (3)	4.9 (4)	3.3(18)
Total	2.9(7)	9.1(10)	1.8(3)	4.9(5)	9.3(13)	10.4(20)	6.2(63)

Analysis of variance table

Source	Sum of squares	d.f.	Mean square	F	P
Within cells	59.471	2,245	0.026	..	..
Regression on age	0.458	1	0.458	17.296	0.001
Between smoking groups[2]	0.504	5	0.101	3.81	0.002
Between behavior types[2]	0.329	1	0.329	12.43	0.001
Interaction	0.396	5	0.079	2.99	0.011

[1] Rates are age-adjusted annual incidence per 1,000 men.

[2] Mean squares for "between smoking groups" and "between behavior types" are each computed eliminating the general mean and the other main effect but ignoring interaction, thus yielding an estimate of each main effect unconfounded by other significant main effects.

Source: Jenkins, C. D. et al. (99).

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TABLE A18.—*Incidence of new coronary heart disease by smoking category and behavior type for men 50–59 years of age*

(Numbers in parentheses are number of CHD cases in each subgroup)

Behavior type	Smoking group					
	Never smoked	Former cigarette smokers	Current and former pipe and cigar only	Cigarettes			Total
				1–15	16–25	26 and over	
A	[1]12.4(5)	18.6(8)	21.8 (8)	16.4(5)	21.6 (9)	30.0(14)	20.4(49)
B	10.0(4)	5.1(1)	8.4 (3)	4.7(1)	21.1 (7)	10.1 (6)	12.0(21)
Total	11.1(9)	14.2(9)	14.9(11)	11.5(6)	21.3(16)	26.0(19)	16.8(70)

Source	Analysis of variance table				
	Sum of squares	d.f.	Mean square	F	P
Within cells	63.527	911	0.070	..	..
Regression on age	0.177	1	0.177	2.54	0.111
Between smoking groups[2]	0.522	5	0.104	1.496	0.188
Between behavior types[2]	0.296	1	0.296	4.24	0.040
Interaction	0.129	5	0.026	0.37	0.870

[1] Rates are age-adjusted annual incidence per 1,000 men.

[2] Mean squares for "between smoking groups" and "between behavior types" are each computed eliminating the general mean and the other main effect but ignoring interaction, thus yielding an estimate of each main effect unconfounded by other significant main effects.

SOURCE: Jenkins, C. D. et al. (*90*).

TABLE A20.—*Experiments concerning the effects of smoking and nicotine on animal cardiovascular function*

Author, year, country, reference	Number and type of population	Smoking procedure	Heart rate	Blood pressure	Cardiac output	Coronary blood flow	Comments
Bellet et al., 1941, U.S.A. (*81*).	39 experiments on dogs which had undergone coronary artery ligation up to 45 days before.	Inhalation of tobacco smoke in chamber.	Definite increase.	Definite increase.			Coronary artery ligation increased the frequency of nicotine-induced severe arrhythmias; these became less evident with increasing time since ligation.
		Nicotine intravenous 0.2-1.2 mg./kg.	Definite increase.	Definite increase.			
Burn and Rand, 1958, England (*85*).	10 rabbits, 5 experimental, 5 control; isolated atria.	Experimental animals pretreated with intraperitoneal nicotine and the atria of both groups excised and perfused with nicotine.					Isolated atrial specimen showed increased rate and increased amplitude of contractions with administration of nicotine proportional to pretreatment. These reactions were blocked by reserpine, and the authors consider nicotine effects to be mediated by catecholamine release from chromaffin store in myocardium.
West et al., 1958, U.S.A. (*208*).	33 normal adult mongrel dogs.	Coronary intra-arterial nicotine: I. 0.2-2.2 μg./kg. II. 0.04-1 μg./kg.	Definite increase (systolic).				I. Myocardial contractility increased 40–90 percent in 15/16 animals tested accompanied by ST segment depression and T-wave inversion and blocked by tetraethylammonium chloride. II. Coronary blood flow increased 19 percent upon left circumflex artery injection; coronary blood flow showed no change upon left anterior descending artery injection, 64 observations on 10 dogs. (Tetraethylammonium chloride blocked CBF increase.) The authors found no evidence of coronary vasoconstriction in these healthy animals.

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TABLE A20.—*Experiments concerning the effects of smoking and nicotine on animal cardiovascular function (cont.)*

Author, year, country, reference	Number and type of population	Smoking procedure	Heart rate	Blood pressure	Cardiac output	Coronary blood flow	Comments
Forte et al., 1960, U.S.A. (65).	27 observations on 8 dogs.	Intravenous nicotine up to 21.5 mg. given as 5–15 μg./kg./minute.		Definite initial increase then decrease.		No change.	No significant change in either left ventricular work or myocardial oxygen extraction.
Kien and Sherrod, 1960, U.S.A. (111).	21 adult dogs	Cigarette smoke under positive pressure via tracheostomy. Nicotine 20 μg./kg. intravenously. Epinephrine 5 μg./kg. intravenously.		Definite increase.	Definite increase.	Increase following increase in blood pressure and cardiac output.	Effects of cigarette smoke were duplicated by intravenous nicotine and epinephrine. During cigarette smoke inhalation, it was noted that without blood pressure or output changes, coronary blood flow did not increase and that while adverse EKG changes were noted they correlated more closely with decreased cardiac oxygen utilization than with actual cardiac work.
Travell et al., 1960, U.S.A. (189).	14 normal rabbits and 18 rabbits with severe cholesterol-induced atherosclerosis.	Intravenous nicotine 0.01–0.1 mg.				Definite increase in normals.	Nicotine-induced coronary blood flow and heart rate increase in the atherosclerotic animals required 10 times and 2 times, respectively, the amounts required in the normal animals.

(65) FORTE, I. E. WILLIAMS, A. J. POTGIETER, L., SCHMITTHENNER, J. E., HAFKENSCHIEL, J. H., RIEGEL, C. Coronary blood flow and cardiac oxygen metabolism during nicotine-induced increases in left ventricular work. Annals of the New York Academy of Sciences 90(1): 174–185, September 27, 1960.

(124) LARSON, R. K., FUKUDA, P., MURRAY, J. F. Systemic and pulmonary vascular effects of nicotine in anesthetized dogs. American Review of Respiratory Diseases 91(4): 556–564. April 1965.

TABLE A20.—*Experiments concerning the effects of smoking and nicotine on animal cardiovascular function (cont.)*

Author, year, country, reference	Number and type of population	Smoking procedure				Comments
Bellet et al., 1962, U.S.A. (22).	I. 10 normal dogs II. 9 dogs at varying intervals following coronary artery ligation. III. 7 dogs with varying grades of artificially-induced coronary artery narrowing.	Intravenous nicotine, 20 μg./kg./minute for 15–20 minutes.			I. 125 percent increase II. 82.6 percent increase III. 83.3 percent increase	The authors noted that: 1. The response of coronary blood flow to nicotine resembled that of anoxemia in the presence of coronary insufficiency. 2. The greater the induced coronary impairment the smaller the increment in coronary blood flow.
Leaders and Long, 1962, U.S.A. (115).	15 adult mongrel dogs.	Left anterior descending intracoronary injection of nicotine or norepinephrine.				Nicotine and norepinephrine both increased coronary vascular resistance and myocardial contractile force (the former measured by a constant-volume variable-pressure system). The action of nicotine was blocked by pretreatment with hexamethonium, pentolinium, reserpine, or guanethidine.
Larson et al., 1965, U.S.A. (124).	13 adult mongrel dogs.	Intravenous nicotine, 0.02 mg./kg./minute for 10–12 minutes.		Definite increase.	Definite increase.	Systemic vascular resistance and pulmonary artery and left atrial pressures showed biphasic responses of increase followed by decrease.

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TABLE A20.—*Experiments concerning the effects of smoking and nicotine on animal cardiovascular function (cont.)*

Author, year, country, reference	Number and type of population	Smoking procedure	Comments
Folle et al., 1966, U.S.A. (64).	7 dogs of 33 investigated (Remainder experienced catheterization failures).	I. Cigarette smoke inhalation to isolated left lower lobe and then blood perfused coronary arteries. II. Cigarette smoke to rest of lung and then blood passed to general circulation. III. Nicotine perfused directly into left coronary artery.	I. No change in coronary vascular resistance. II. 5/6 showed increase in coronary vascular resistance due, according to the author, to general sympathetic nervous system stimulation. III. 4/5 showed increase in coronary vascular resistance. The authors conclude that the cardiac effects of tobacco arise almost entirely from the extracardiac actions of smoking instead of the direct response of the heart.
Nadeau and James, 1967, U.S.A. (148).	26 dogs	Nicotine 0.01–10.0 μg. into sinus node artery.	Heart rate showed initial slowing (due probably to vagal stimulation) followed by acceleration (due probably to vagal paralysis and catecholamine release). No systemic blood pressure changes noted.
Romero and Talesnik, 1967, U.S.A. (156).	16 experiments on isolated cat heart.	Nicotine in varying doses in perfusate of coronary arteries.	Over 5 μg. of nicotine was found to produce an initial bradycardia associated with increased coronary flow, followed by prolonged tachycardia with an initial decrease in coronary blood flow followed by a prolonged increase. Pretreatment with hexamethonium or reserpine prevented both the myocardial stimulation and the increase in coronary blood flow. The authors consider the action of nicotine to be a combination of a direct vasoconstrictive effect and an indirect catecholamine-releasing vasodilating effect.
Puri et al., 1968, U.S.A. (153).	12 mongrel dogs	I. (14) Intravenous nicotine 50 μg./kg./minute for 3–4 minutes II. (8) Propranolol pretreatment, then 50 μg./kg./minute nicotine for 3–4 minutes	I. Nicotine produced a definite increase in the force and velocity of left ventricular contraction. II. Pretreatment with propranolol produced (relative to results of Group 1): (a) A further increase in left ventricular systolic pressure. (b) A decrease in velocity of shortening. (c) A significant increase in left ventricular end-diastolic pressure. The authors conclude that propranolol probably impairs the norepinephrine-like effects of nicotine on the myocardium while enhancing its peripheral vasopressor effects.

(64) FOLLE, L. E., SAMANEK, M., AVIADO, D. M. Cardiopulmonary effects of tobacco and related substances. II. Coronary vascular effects of cigarette smoke and nicotine. Archives of Environmental Health 12(6): 712–715. June 1966.

(152) PURI, P. S., ALAMY, D., BING, R. J. Effect of nicotine on contractility of the intact heart. Journal of Clinical Pharmacology 8(5): 295–301, September–October 1968.

TABLE A20.—*Experiments concerning the effects of smoking and nicotine on animal cardiovascular function (cont.)*

Author, year, country, reference	Number and type of population	Smoking procedure	Comments
Balazs et al., 1963, U.S.A. (16).	Beagle dogs with lesions induced in myocardium by either: (1) Isoproterenol pretreatment, or (2) ligation of the anterior descending coronary artery.	I. Normals (3–6 per experiment): (a) 4 μg./kg. intravenous nicotine, (b) 40 μg./kg. intravenous nicotine. II. Experimental (3): 4 μg./kg. intravenous nicotine	I. (a) No evidence of arrhythmias; (b) A single or a few ectopic beats in 2/3 normal dogs. II. Extrasystoles noted in 2/3 animals during the first day after cessation of the arrhythmia induced by the lesion alone, but not thereafter. These and nicotine-induced arrhythmias were of a short duration.
Greenspan et al., 1969, U.S.A. (74).	Cardiac muscle isolated from the right ventricle of 10 adult dogs.	Nicotine 2–100 μg./cc. in Tyrode's solution perfusate.	Nicotine perfusion produced: (1) An increase in myocardial contractile force apparently independent of adrenergic innervation. (2) An increased automaticity of the Purkinje fiber system apparently due to release of catecholamines from chromaffin tissue stores. (3) A decrease in conduction velocity. The authors conclude that the latter two effects probably predispose to arrhythmia formation.
Saphir and Rapaport, 1969, U.S.A. (166).	88 mongrel cats	Nicotine 5–12 μg./kg. injected intraarterially to mesenteric circulation.	I. Mesenteric injection of nicotine was followed with 1–2 seconds by: (a) Increased left ventricular systolic pressure (LVSP). (b) Increased systemic resistance. (c) Enhanced myocardial performance. II. Left ventricular injection of nicotine was followed by: (a) Increased LVSP. (b) Bradycardia. (c) Enhanced myocardial performance greater than that seen in mesenteric-injected group. III. Pretreatment with phenoxybenzamine diminished the increase in LVSP while propranolol pretreatment diminished the enhancement of myocardial performance while LVSP still showed a significant increase. IV. Mesenteric sympathetic nerve section led to a diminished response. The authors conclude that the cardiovascular responses to nicotine may be neurogenic in nature with receptors distributed in certain abdominal arteries.

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TABLE A20.—*Experiments concerning the effects of smoking and nicotine on animal cardiovascular function (cont.)*

Author, year, country, reference	Number and type of population	Smoking procedure	Comments
Leb et al., 1970, U.S.A. (*158*).	12 mongrel dogs and CBF measured with use of Rb^{86} and digital counter.	Nicotine 100 μg./kg. for 1 minute intravenously.	Effective Coronary Flow (ECF) is that part of the total coronary flow (TCF) which is "effectively" involved in nutrient exchange. Nicotine injection was followed by: (1) 95.6 percent increase in TCF. (2) 61.1 percent increase in ECF. (3) 73.1 percent increase in myocardial oxygen consumption and analysis revealed that capillary flow increased almost proportionately to myocardial oxygen consumption whereas the increase in TCF was far in excess. (4) Definite increases in cardiac output, heart rate, left ventricular work, and aortic pressure.
Ross and Biess, 1970, U.S.A. (*169*).	10 dogs undergoing instantaneous coronary arterial flow measurement.	Nicotine 10–100 μg. intracoronary injection.	Nicotine injection was followed by: (1) Increased contractile force. (2) Decreased myocardial contraction time. (3) Decreased time necessary to reach peak tension. (4) Decreased total stroke systolic CBF. (5) Increased total stroke diastolic CBF. (6) Increased total stroke CBF. (7) Changes similar to intraarterial epinephrine. (8) Changes blocked by pentolinium pretreatment. (9) No change in heart rate or blood pressure. The authors conclude that catecholamines released from the ventricular myocardium mediated these responses to nicotine.

TABLE A21.—*Experiments concerning the effects of smoking and nicotine on the cardiovascular system of humans*

Author, year, country, reference	Number and type of population	Smoking procedure	Heart rate	Blood pressure	Electrocardiogram ballistocardiogram	Stroke volume	Cardiac output	Coronary blood flow	Comments
Russek et al., 1955, U.S.A. (*164*).	I. 23 healthy male smokers 21–40 years of age (average 42). II. 37 male patients with overt clinical CHD 42–70 years of age (average 54), 6 were nonsmokers.	1 standard and 1 denicotinized cigarette.	I. Increase. II. Increase.	Increase. Increase.	EKG: I. 16/23 showed significant changes. II. No significant changes. BCG: I. ... II. 18/37 showed significant change.				Denicotinized cigarettes evoked changes of a lesser degree in normals and CHD subjects, but in the latter group there was no significant difference between these changes.
Bargeron et al., 1957, U.S.A. (*17*).	16 of 30 healthy adult male volunteer smokers and nonsmokers who underwent successful catheterization 18–63 years of age.	1 cigarette inhaled at intervals of 20 seconds.	Insignificant increase.	Increase.				Definite increase.	Coronary vascular resistance fell significantly. Myocardial O_2 usage underwent no significant change. Pyruvate extraction fell slightly. Authors consider lack of increase in heart rate as due to baseline apprehensive tachycardia.

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TABLE A21.—*Experiments concerning the effects of smoking and nicotine on the cardiovascular system of humans (cont.)*

Author, year, country, reference	Number and type of population	Smoking procedure	Heart rate	Blood pressure	Electrocardiogram ballistocardiogram	Stroke volume	Cardiac output	Coronary blood flow	Comments
Regan et al., 1960, U.S.A. (151).	7 males with history of EKG-proven myocardial infarction undergoing cardiac catheterization.	2 standard cigarettes in 25 minutes inhaled at minute intervals.	Definite increase.	Definite increase.			Increase.	No significant change.	Myocardial O_2 consumption rose slightly in 3 out of 7. The author considers that the EKG changes noted on smoking are probably due less to decreased coronary blood flow than to increased workload (oxygen need) where oxygen supply does not increase. Noted no evidence of myocardial ischemia during smoking.
Thomas and Murphy, 1960, U.S.A. (186).	113 clinically healthy young males.	One standard cigarette smoked at own pace.	Definite increase.	Definite increase.		Definite increase.	Definite increase.		Pulse pressure showed a decrease. Smokers responded slightly but significantly more actively than non-smokers. ECG changes were increasingly common with increasing age, weight, and serum cholesterol.

(186) THOMAS, C. B., MURPHY, E. A. Circulatory responses to smoking in healthy young men. Annals of the New York Academy of Sciences 90(1): 266–276, September 27, 1960.

TABLE A21.—*Experiments concerning the effects of smoking and nicotine on the cardiovascular system of humans (cont.)*

Author, year, country, reference	Number and type of population	Smoking procedure	Heart rate	Blood pressure	Electrocardiogram ballistocardiogram	Stroke volume	Cardiac output	Coronary blood flow	Comments
Von Ahn, 1960, Sweden (201).	The author reviews a series of experiments performed between 1944–1956.	Cigarette smoking.	Increase.		EKG: Slight ST segment depression and T-wave flattening.				EKG changes more prominent in young, clinically healthy subjects than in older, habitual smokers. Intravenous nicotine and smoking showed identical cardiovascular effects. Smoking elicited angina pectoris in a number of CHD patients.
Irving and Yamamoto, 1962, England (89).	6 normal males, 15 patients with diseases not defined, 19–66 years of age, all moderate-heavy cigarette smokers.	(a) Sham smoking. (b) Non-inhalation smoking. (c) 2 standard cigarettes in 10 minutes. (d) Nicotine 0.6 mg. intravenously.	(a) No change. (b) No change. (c) Definite increase. (d) Definite increase.	No change. No change. Widened pulse pressure. Definite increase.		(a) No change. (b) No change. (c) Definite increase. (d) Definite increase.	No change. No change. Definite increase. Definite change.		Cardiac output measured by dye dilution technique.

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TABLE A21.—*Experiments concerning the effects of smoking and nicotine on the cardiovascular system of humans (cont.)*

Author, year, country, reference	Number and type of population	Smoking procedure	Heart rate	Blood pressure	Electrocardiogram ballistocardiogram	Stroke volume	Cardiac output	Coronary blood flow	Comments
Pentecost and Shillingford, 1954, U.S.A. (149).	I. 14 volunteers with clinical CHD, 13/14 smokers, average age 39.5.	Single cigarette smoked at own rate in 6–7 minutes.	Definite increase in all groups.	Definite increase in all groups.		I. 10 percent increase.	37 percent increase.		
	II. 6 patients with angina pectoris, all smokers, average age 43.4.					II. Intermediate change.	Intermediate change.		
	III. 14 patients with history of definite myocardial infarction, all smokers average age 54.1.					III. 8 percent decrease.	1 percent increase.		
Frankl et al., 1965, U.S.A. (67).	6 male and 3 female patients with healed myocardial infarction 48–69 years of age 2/8 nonsmokers.	2 standard cigarettes in 10 minutes at rest and under graded exercise.	Definite increase at rest and at exercise.			No significant changes at rest or during exercise.	No significant changes at rest or during exercise.		The author contrasts this response with that seen among healthy young individuals.

(171) SEN GUPTA, A. N., GHOSH, B. P. Observations on some cardiovascular and biochemical effects of tobacco smoking in health and in ischaemic cardiacs. Bulletin of the Institute of Post-Graduate Medical Education and Research 9(2): 45–57, April 1967.

TABLE A21.—*Experiments concerning the effects of smoking and nicotine on the cardiovascular system of humans (cont.)*

Author, year, country, reference	Number and type of population	Smoking procedure	Heart rate	Blood pressure	Electrocardiogram ballistocardiogram	Stroke volume	Cardiac output	Coronary blood flow	Comments
Sen Gupta and Ghosh, 1967, India (171).	6 healthy male nonsmokers.	1 untipped cigarette in 5–7 minutes.	Increase in all groups.	Increase in all groups.	No change.				
	8 healthy male smokers.				6/8 showed ST changes.				
	6 patients with CHD, nonsmokers.				All showed ST and T-wave changes.				
	5 patients with CHD, smokers.				All showed ST and T-wave changes.				
	36–64 years of age.								
Aronow et al., 1968, U.S.A. (5).	10 male patients with classical angina pectoris. 32–59 years of age	1 standard high nicotine cigarette in 5 minutes.	Definite increase.	Definite increase.					Product of systolic blood pressure and heart rate showed a significant increase on smoking while left ventricular ejection time values did not. All patients developed angina more rapidly under a constant exercise load if they had smoked before exercising.
Kerrigan et al., 1968, U.S.A. (102).	24 male and 1 female healthy smokers, average age, 45.	2 filtered cigarettes in 15 minutes with measures taken at rest and during exercise.	Definite increase under rest and exercise conditions.	Definite increase under rest and exercise conditions.			Cardiac index. Definite increase under rest and exercise conditions.		The increase in cardiac index, heart rate, and blood pressure during exercise with smoking was the sum of such increases seen with smoking or exercise separately. Neither group showed increases in peripheral vascular resistance.
	8 male and 2 female healthy nonsmokers, average age 33.								

(5) ARONOW, W. S., KAPLAN, M. A., JACOB, D. Tobacco: A precipitating factor in angina pectoris. Annals of Internal Medicine 69(3): 529–536, September 1968.

(102) KERRIGAN, R., JAIN, A. C., DOYLE, J. T. The circulatory response to cigarette smoking at rest and after exercise. American Journal of the Medical Sciences 255(2): 113–119, February 1968.

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TABLE A21.—*Experiments concerning the effects of smoking and nicotine on the cardiovascular system of humans (cont.)*

Author, year, country, reference	Number and type of population	Smoking procedure	Heart rate	Blood pressure	Electrocardiogram ballistocardiogram	Stroke volume	Cardiac output	Coronary blood flow	Comments
Allison and Roth, 1969, U.S.A. (5).	30 healthy male subjects. 32–59 years of age.	2 standard cigarettes smoked in 12–16 minute period.	Definite increase.	Increase.			Increase followed by decrease within 20 minutes.		Definite decrease in pulmonary blood volume as indicated by impedance methods of thoracic pulse volume.
Aronow and Swanson, 1969, U.S.A. (7).	10 male patients with classical angina pectoris. 32–59 years of age.	1 low nicotine cigarette in 5 minutes.	Definite increase.	Definite increase.					All patients developed angina sooner if they smoked before exercising.
Aronow and Swanson, 1969, U.S.A. (6).	10 male patients with classical angina pectoris. 32–59 years of age.	1 non-nicotine cigarette in 5 minutes.	No change.	No change.					No difference noted in time or onset of exercise-induced angina between smoking and non-smoking procedures.
Marshall et al., 1969, U.S.A. (129).	42 normotensive healthy male prisoners 18–50 years of age. 13 nonsmokers. 16 moderate smokers. 13 heavy smokers.	3/4 of one standard cigarette.	Insignificant increase.	Insignificant increase.					Blood pressure response to cold pressor test noted to be greater in heavy smokers. Presyncopal reactions to 40 degree head-up tilt more frequent in smokers.

(5) ALLISON, R. D., ROTH, G. M. Central and peripheral vascular effects during cigarette smoking. Archives of Environmental Health 19(2): 189–198, August 1969.

(7) ARONOW, W. S., SWANSON, A. J. The effect of low-nicotine cigarettes on angina pectoris. Annals of Internal Medicine 71(3): 599–601, September 1969.

(6) ARONOW, W. S., SWANSON, A. J. Non-nicotinized cigarettes and angina pectoris. Annals of Internal Medicine 70(6): 1227, June 1969.

(129) MARSHALL, W. J., JR., STANLEY, E. L., KEZDI, P. Cardiovascular effects of cold pressor tests, 40° head-up tilt, and smoking on smokers and nonsmokers. Diseases of the Chest 56(4): 290–296, October 1969.

TABLE A22.—*Experiments concerning the effect of nicotine or smoking on catecholamine levels*

Author, year, country, reference	Number and type of subject	Procedure	Results
Watts, 1960, U.S.A. (203).	11 dogs	0.02–0.60 mg/kg. nicotine intravenously.	Nicotine administration was associated with significant increases in peripheral arterial epinephrine levels. Ganglionic blocking agents prevented this effect.
Westfall and Watts, 1963, U.S.A. (210).	22 mongrel dogs	Cigarette smoking via tracheal cannula; 1 cigarette/8 minutes for 35 minutes.	Regular cigarette smoke evoked a statistically significant increase in adrenal vein, vena cava, and femoral artery levels of epinephrine. Cornsilk cigarette smoke evoked no change.
Westfall and Watts, 1964, U.S.A. (211).	21 male volunteers approximately 25 years of age; 11 nonsmokers, 10 smokers.	3 cigarettes smoked in 30 minutes.	Smoking at rate noted for 2½ hours evoked a significant increase in urinary epinephrine, but not norepinephrine levels.
Westfall et al., 1966, U.S.A. (208).	Mongrel dogs	Standard cigarette smoke exposure via endotracheal tube. Smoke inhalation every third inspiration for 8 minutes.	Smoke inhalation evoked a rise in cardiac output, stroke volume, blood pressure, and plasma catecholamine levels. Pretreatment with propranolol diminished the cardiac output and stroke volume responses but increased the blood pressure response—the latter effect due to the release of alpha-receptor activity by beta-blockade.

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Author, year, country, reference	Number and type of animal	Procedure	Results
Adler et al., 1906, U.S.A. (*2*).	Rabbits	Nicotine 1.5 mg. intravenously in 6 percent solution 6 of 7 days per week for more than 4 months.	The authors noted an arteriionecrosis of the aorta, affecting mainly the inner muscular layers. Macroscopically, early changes consisted of small areas of calcareous ridging and aneurysmal dilatation without notable fatty degeneration or intimal discontinuity. Microscopically, early changes appeared in the muscle cells of the media, and "chalky" deposits were noted between the elastic fibers.
Hueper, 1943, U.S.A. (*86*).	I. 6 mongrel dogs.	Nicotine subcutaneously. Increasing dosage up to 2.5 cc. of 3 percent solution for 1 month.	I. 4/6 animals died of infection and showed marked edema and focal hyalinization of the media of the aorta and large elastic arteries. 2/6 animals were sacrificed and showed thickening and hyalinization of the walls of the coronary arteries and edema of the media as well as endothelial proliferation of other arteries.
	II. 40 rats.	Increasing doses up to 1 cc. of 1 percent solution for 1 month.	II. Much less aortic involvement than that found in the dogs; infrequent arteriolar changes consisting of fibrosis and thickening of the media.
Maslova, 1956, USSR (*130*).	Rabbits	I. (10) Nicotine subcutaneously 1 percent solution 0.2 cc. daily for 115 days. II. (14) Nicotine plus 0.2 grams cholesterol per day. III. (10) Cholesterol only.	I. Aortic wall—acute swelling of elastic fibers with focal fragmentation and partial disintegration—no intimal fat deposits seen. Coronary vessels—thickening of the vessel wall—no fat deposits. II. Aorta—"massive" deposits of "cholesterol" in the intima and vasa vasorum with "loosening" of the aortic wall. Coronary vessels—the larger vessels showed moderate fat deposition and the smaller vessels showed swelling of the elastica. III. Aorta—isolated lipid deposition in the arch and ascending portions only. Coronary vessels—no fat deposition.
Czochra-Lyszewicz et al., 1959, U.S.A. (*46*).	Rabbits	I. (10) 1.0 g. cholesterol/day for 100 days. II. (10) Cholesterol plus 0.0015 g. nicotine/day intravenously. III. (4) Nicotine only.	Index of aortic lesion density (cholesterol infiltration): I. 2.6. II. 3.6. III. No aortic lesions noted.

(*2*) ADLER, I., HENSEL, O. Intravenous injections of nicotine and their effects upon the aorta of rabbits. Journal of Medical Research 15: 229–239, 1906.

(*86*) HUEPER, W. C. Experimental studies in cardiovascular pathology. VII. Chronic nicotine poisoning in rats and in dogs. A.M.A. Archives of Pathology 35: 846–856, 1943.

(*164*) THIENES, C. H. Chronic nicotine poisoning. Annals of the New York Academy of Sciences 90(1): 239–248, September 27, 1960.

TABLE A23.—*Experiments concerning the atherogenic effect of nicotine administration (cont.)*

Author, year, country, reference	Number and type of animal	Procedure	Results
Wenzel et al., 1959, U.S.A. (*187*).	Rabbits	I. (12) Control untreated. II. (12) Control diet plus 1 percent cholesterol and 5 percent cottonseed oil added. III. (12) Control diet plus oral nicotine 2.28 mg./kg./day. IV. (12) Regimen II plus oral nicotine 2.28 mg./kg./day. V. (12) Regimen II plus oral nicotine 1.42 mg./kg./day. VI. (12) Regimen II plus oral nicotine 0.57 mg./kg./day.	General findings: Marked aortic pathologic involvement was noted in all cholesterol-treated groups; however, no difference was noted between Group II. and Groups IV., V., and VI. Cardiac histopathology: I. No change. II. Advanced atherosclerotic changes in the subendocardial vessels. III. Thickening and fibrosis of coronary artery small branches. IV.–VI. More severe changes with greater fatty metamorphosis and actual early myocardial necrosis, but no dose-dependent effects observed.
Thienes 1960, U.S.A. (*164*).	Newborn rats and mice.	Nicotine subcutaneously up to 5 mg./kg. twice daily by the end of 1 month. Animals autopsied at 1 year.	No arterial pathology noted. Medial degeneration seen more frequently in controls. Suggests that older animals be used.
Grosgogeat et al., 1965, France (*75*).	Male rabbits	I. (10) Nicotine subcutaneously 0.75 mg./day. (10) Controls—saline injected. Sacrificed at from 20–120 days. II. (27) Same as Group I. (27) Controls—saline injected. Sacrificed at 90 days. III. (66) Nicotine subcutaneously 0.3–1.5 mg./day. Sacrificed at 30 days. IV. (24) Nicotine subcutaneously 0.75 mg./day. (24) Controls—saline injected. One-half of each group ate cholesterol-enriched diet (0.5–1.0 percent cholesterol added). Sacrificed at 60 days.	Significant differences in aortic subendothelial fibrosis between control and experimental groups noted only in II and IV. In group IV, the nicotine-treated group showed more severe changes.

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(Table A24.—Experiments concerning the atherogenic effect of nicotine administration (cont.))

Author, year, country, reference	Number and type of animal	Procedure			Results
		Nicotine	*Diet*	*Vitamin D*	
Hass et al., 1956, U.S.A. (*80*).	Male rabbits	I. (8) Control II. (7) Control III. (14) Nicotine IV. (15) Nicotine V. (9) Control VI. (14) Nicotine (Sacrificed at various times) Control—no treatment. Nicotine—subcutaneous injections in oil—increasing amounts 2 times per week. Vitamin D—subcutaneous injections up to 6–8 x 10^6 IU. Cholesterol—250–500 mg. cholesterol added per 100 g. diet.	Control Cholesterol Control Cholesterol Cholesterol Cholesterol	Control Control Control Control Vitamin D Vitamin D	I. Infrequent medial calcific disease without lipid localization. II. No medial calcific disease but frequent intimal atheroma formation. III. Rare calcific medial degeneration; no intimal atheromatous disease. IV. The largest number of atheromatous lesions. V. No medial calcific disease. VI. Consistent medial calcific disease.
Choi, 1967, Korea (*48*).	Albino rabbits	I. Nicotine 1–5 mg./kg./day intraperitoneally. Cholesterol 1 g./day (in varying combinations with controls). II. Nicotine alone. III. Cholesterol alone. (Sacrificed at 60 days)			I. Increasing nicotine dosages were associated with decreased atheroma formation (findings not statistically significant). II. Nicotine alone produced no atheroma formation but was associated with the presence of aortic medial calcification and endothelial hyperplasia. III. Cholesterol alone was associated with a definite increase in atheroma formation.
Stefanovich et al., 1969, U.S.A. (*178*).	Female albino rabbits.	I. (10) Diet supplemented with 2.0 percent cholesterol. Nicotine intramuscularly 2.78 mg./kg./day, 5/7 days. II. (10) Cholesterol only. III. (10) Nicotine only. IV. (10) Control.	*Percent of aortic surface involved with atherosclerosis* I. 9.4 II. 6.7 III. 0.1 IV. ..		In both stock and cholesterol-fed animals, nicotine was also noted to increase aortic triglyceride content and to decrease aortic free cholesterol content.

(*147*) Page, I. H., Lewis, L. A., Moinuddin, M. Effect of cigarette smoking on serum cholesterol and lipoprotein concentrations. Journal of the American Medical Association 171(11): 1500–1502, November 14, 1959.

(*104*) Kershbaum, A., Bellet, S., Dickstein, E. R., Feinberg, L. J. Effect of cigarette smoking and nicotine on serum free fatty acids. Based on a study in the human subject and the experimental animal. Circulation Research 9(3): 631–635, May 1961.

(*103*) Kershbaum, A., Bellet, S., Caplan, R. F., Feinberg, L. J. Effect of cigarette smoking on free fatty acids in patients with healed myocardial infarction. American Journal of Cardiology 10(2): 204–208, August 1962.

ATLE A25.—*Experiments concerning the effect of smoking and nicotine upon blood lipids*
(Human Studies)

Author, year, country, reference	Number and type of population	Smoking procedure	Plasma free fatty acids	Serum cholesterol	Serum triglycerides	Other	Comments
Page et al., 1959, U.S.A. (*147*).	13 male and 7 female laboratory workers 17–51 years of age.	2 nonfiltered cigarettes in 10 minutes and blood levels measured over 30-minute period.		No change.		*Serum lipoproteins* No change (10 subjects).	
Kershbaum et al., 1961, U.S.A. (*104*).	31 male patients or staff 16–72 years of age. 7 normals, 7 CHD, 17 other medical diagnoses.	I. 17 subjects smoked 2 non-filter cigarettes in 10 minutes. II. 9 controls. III. 5 subjects smoked 5 cigarettes in 40 minutes.	*Mean rise* I. 351 μEq./L. II. 9.8 μEq./L. III. 272–2,304 μEq./L.	No change.	No change.		The authors consider the increase among controls to be due to fasting.
Kershbaum et al., 1962, U.S.A. (*103*).	I. 17 male patients with healed myocardial infarctions. II. 16 non-CHD patients. III. 10 normals. IV. 13 normals.	I., II., III., 2 non-filter cigarettes in 10 minutes. IV. No smoking.	*Mean rise* I. 865 μEq./L. II. 320 μEq./L. III. 232 μEq./L. IV. 20 μEq./L.				No difference found between results following inhalation or noninhalation. Statistically significant difference found between increases in Groups II and III and Group I.

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TABLE A25.—*Experiments concerning the effect of smoking and nicotine upon blood lipids (cont.)*

(Human Studies)

[SM = Smokers NS = Nonsmokers]

Author, year, country, reference	Number and type of population	Smoking procedure	Plasma free fatty acids	Serum cholesterol	Serum triglycerides	Other	Comments
Kershbaum et al., 1963, U.S.A. (*109*).	11 normal patients.	9 standard cigarettes in 3 hours. Samples at 10, 20, and 40 minutes of smoking period.	Definite increase at start of smoking period.			8 patients with trimethaphan camphorsulfonate (Arfonad) pretreatment and 8 formerly adrenalectomized patients showed either minimal or no elevation.	Both free and total urinary catecholamines increased with smoking and the author considers them as mediators of the FFA increase.
Knuttinen and Rajasalmi, 1963, Finland (*110*).	40 healthy moderate smokers 19–20 years of age.	Fed at fat meal and then 20 were allowed to smoke cigarettes of known-nicotine content over 6 hour period (approximately 23 cigarettes consumed).	NS—definite increase at 6 hours. SM—definite increase at 6 hours.	No change in either group.	NS—definite increase at 2 hours. SM—slight increase at 2 hours.		
Kedra et al., 1965, Poland (*101*).	37 male and 5 female medical students 22–23 years of age.	3 cigarettes smoked in rapid succession and samples taken at 10 and 30 minutes.	No change.	No change.		Beta-lipoproteins definite increase.	

(*110*) KONTTINEN, A., RAJASALMI, M. Effect of heavy cigarette smoking on post-prandial triglycerides, free fatty acids, and cholesterol. British Medical Journal 1(5334): 850–852, March 30, 1963.

(*101*) KEDRA, M., POLESZAK, J., PITERA, A. Wplyw palenia tytoniu na poziom tluszczowcow krwi. (Influence of tobacco smoking on the blood lipid levels.) Polski Tygodnik Lekarski 20(39): 1452–1454, September 27, 1965.

(*205*) WENZEL, D. G. BECKLOFF, G. L. The effect of nicotine on experimental hypercholesterolemia in the rabbit. Journal of the American Pharmaceutical Association; Scientific Edition 47(5): 338–343. May 1958

(*107*) KERSHBAUM, A., BELLET, S., KHORSANDIAN, R. Elevation of serum cholesterol after administration of nicotine. American Heart Journal 69(2): 206–210, February 1965.

TABLE A25a.—*Experiments concerning the effect of smoking and nicotine upon blood lipids*

(Animal Studies)

ANIMAL AND IN VITRO STUDIES

Author, year, country, reference	Number and type of population	Smoking procedure	Plasma free fatty acids	Serum cholesterol	Serum triglycerides	Other	Comments
Wenzel and Beckloff, 1958, U.S.A. (*205*).	48 male New Zealand white rabbits.	I. Untreated control—12 subjects. II. Regular diet plus 0.1 percent cholesterol—12 subjects. III. Regular diet plus 2.28 mg./kg./day nicotine in water—12 subjects. IV. Diet plus— (a) 0.1 percent cholesterol (b) 2.28 mg./kg./day nicotine in water—12 subjects.				Group II and IV showed an immediate increase in plasma cholesterol and phospholipids with a leveling of response at 4 weeks. Group IV showed a further increase at 8–12 week period.	The authors consider an elevated cholesterol/ phospholipid ratio to be a notable indication of atherogenic susceptibility. The concomitant increase in phospholipids with the cholesterol may negate the importance of nicotine-induced hypercholesterolemia as an atherogenic stimulus.
Kershbaum et al., 1961, U.S.A. (*104*).	8 mongrel dogs.	Intravenous infusion of 20 mg./kg. nicotine in 20 minutes.	Definite increase in 12/15 observations.				
Kershbaum et al., 1965, U.S.A. (*107*).	20 adult mongrel dogs.	I. 9 received IM nicotine daily for 6 weeks; up to 1 mg./kg. II. 5 placebo injection. III. 6 control.	I. Significant increase in 8/9 dogs. II. No change. III. No change.		No change in any group.		

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TABLE A25a.—*Experiments concerning the effect of smoking and nicotine upon blood lipids* (cont.)
(Animal Studies)

ANIMAL AND IN VITRO STUDIES

Author, year, country, reference	Number and type of population	Smoking procedure	Serum triglycerides	Plasma free fatty acids	Serum cholesterol	Other	Comments
Kershbaum et al., 1966, U.S.A. (*108*).	28 adult mongrel dogs.	Intravenous infusion of nicotine.		No change.			The authors report on the results of the use of nethalide (a Beta-adrenergic blocker), phenoxybenzamine, and chlorpromazine to block the FFA response to nicotine. Only nethalide was successful and this constitutes an indication that nicotine stimulates beta-adrenergic receptors to release catecholamines which, in turn, stimulate the release of FFA.
Kershbaum et al., 1967, U.S.A. (*110*).	Sprague-Dawley rat fat-pad tissue.	Nicotine perfusion.					Although nicotine perfusion was not associated with FFA release from fat tissue, epinephrine did produce a significant increase in FFA release. The authors conclude that the sympathetic nervous system mediates the FFA response to nicotine in the intact animal.

(*115*) KJELDSEN, K., DAMGAARD, F. Influence of prolonged carbon monoxide exposure and altitude hypoxia on serum lipids in man. Scandinavian Journal of Clinical and Laboratory Investigation 22 (Supplementum 103): 16–19, 1968.

TABLE A26.—*Experiments concerning the effect of carbon monoxide exposure upon blood lipids*

Author, year, country, reference	Number and type of population	Smoking procedure	Results
Kjeldsen and Damgaard 1968, Denmark (*115*).	8 male students 23–27 years of age.	Five daily one-half hour exposures to 0.5 percent CO for 8–10 days. Overall mean COHb resulting was 12.5 percent.	No significant changes in total fatty acids, phospholipids, or triglycerides. Cholesterol showed a significant increase only during the last 3 days of exposure.
Kjeldsen, 1969, Denmark (*113*).	72 female albino rabbits: I. Regular diet, 24 subjects. II. Regular diet plus 2 percent cholesterol, 24 subjects. III. Regular diet plus 2 percent cholesterol, 24 subjects.	I. 12 control and 12 exposed to gradually increasing CO concentrations (0.015–0.40 percent) over a 4-week period. II. 12 control and 12 exposed to 0.020 percent CO for 35 days. III. 12 control and 12 exposed to to 0.020 percent CO for 7 weeks, then 0.036 percent CO for 3 weeks.	I. Serum cholesterol concentrations rose rapidly and then remained slightly above control values for the 4-week period. II. At 35 days, the serum cholesterol concentration in the exposed group was 2½ times that in the control group. III. Serum cholesterol concentrations among those exposed were significantly higher than those in the control group for 6 weeks of the 10-week period.
Kjeldsen, 1969, Denmark (*113*).	24 castrated male albino rabbits. Regular diet plus 2 percent cholesterol.	12 control and 12 maintained at 10 percent oxygen levels for 6 weeks, then 9 percent for 2 weeks.	Serum cholesterol and triglyceride concentrations rose to significantly higher levels during 3 of the 8 weeks. No changes noted in serum phospholipids.

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TABLE A26.—*Smoking and thrombosis*

Author, year, country, reference	Number and type of population	Experimental conditions[a]	Whole blood clotting time	Prothrombin time	Partial thromboplastin time	Recalcified plasma clotting time	Platelet adhesiveness	Platelet count	Platelet survival	Platelet turnover	Other	Comments
Blackburn et al., 1959, U.S.A. (25).	16 adult schizophrenic patients, 3 university students, all smokers.	12 individuals smoked 2 high-nicotine standard brand cigarettes.									*Plasma stypven time* (−)	
Mustard and Murphy, 1963, U.S.A. (141).	7 white males with either CVD or COPD, all heavy smokers 35–72 years of age.	Compared after periods of abstinence or continuation of smoking.	(−)	(−)	(−)		(−)	(−)	(+) decrease	(+) increase	*Platelet clumping time* (±)	
Ambrus and Mink, 1964, U.S.A. (4).	20 healthy male non-smoking medical students <30 years of age.	Deep inhalation of one nonfiltered cigarette.	(−)		(−)	(−)	(±) increase	(−)			*Thromboplastin generation time* (−)	2 students became ill. Results reflect data on 18.
Ashby et al., 1965, Ireland (8).	27 male medical students and hospital staff members.	13 controls measured at 2 separate times 14 subjects measured before and after smoking 2 cigarettes in 20 minutes.					(+) increase					Increase of subjects greater than that of controls at $p<0.01$.

TABLE A27.—*Smoking and thrombosis (cont.)*

Author, year, country, reference	Number and type of population	Experimental conditions[a]	Whole blood clotting time	Prothrombin time	Partial thromboplastin time	Recalcified plasma clotting time	Platelet adhesiveness	Platelet count	Platelet survival	Platelet turnover	Other	Comments
Bagai and Joshi, 1965, India (174).	11 observations on male smokers all regular tobacco users.	Smoked 2 cigarettes or 2 biris or chewed 1 betel nut quid in 20 minutes.	(−)	(−)		(−)	(+) increase				*Fibrinolysis* (+) decrease	biri—tobacco wrapped in tobacco leaf.
Engelberg, 1965, U.S.A. (58).	40 male and 20 female hospital patients, all smokers 17–68 years of age.	2 cigarettes in 20 minutes.									*Chandler (in vitro) thrombosis time* + decrease	
Kedra and Kocelko, 1965, Poland (100).	39 male and 11 female smokers and 24 male and 26 female nonsmokers 16–45 years of age.	6 cigarettes in 1 hour.	(±) decrease	(−)		(+) decrease					*Thrombin time* (±) decrease	
Murchison and Fyfe, 1966, Scotland (138).	8 males and 4 female patients with various diseases, all heavy smokers 17–67 years of age.	2 cigarettes in 15 minutes, 5f or unfil cigarettes.					(↑)	(+) increase				[a] Smoking both fil and unfil cigarettes caused a rise in platelet adhesiveness which the authors correlated with rise in plasma nonesterified fatty acids.

(25) BLACKBURN, H., JR., ORSIA, E., HARTEL G., PUNSAR, S. Tobacco smoking and blood coagulation: Acute effect on plasma Stypven time. American Journal of the Medical Sciences 238: 448–451, October 1959.

(141) MUSTARD, J. F., MURPHY, E. A. Effect of smoking on blood coagulation and platelet survival in man. British Medical Journal 1(5334): 846–849, March 30, 1963.

(4) AMBRUS, J. L., MINK, I. B. Effect of cigarette smoking on blood coagulation. Clinical Pharmacology and Therapeutics 5(4): 428–431, 1964.

(8) ASHBY, P., DALBY, A. M., MILLAR, J. H. D. Smoking and platelet stickiness. Lancet 2: 158–159, July 24, 1965.

(174) SOCANI, R. K., JOSHI, K. C. Effect of cigarette and biri smoking and tobacco chewing on blood coagulation and fibrinolytic activity. Indian Heart Journal 17: 238–242, July 1965.

(58) ENGELBERG, H. Cigarette smoking and the *in vitro* thrombosis of human blood. Journal of the American Medical Association 193(12): 1033–1035, September 20, 1965.

(100) KEDRA, M., KOCIELKO, A. Tobacco smoking and blood clotting. Bulletin of Polish Medical Science and History 8: 145–148, October 1965.

(138) MURCHISON, L. E., FYFE, T. Effects of cigarette smoking on serum-lipids, blood-glucose, and platelet adhesiveness. Lancet 2(7456): 122–124, July 23, 1966.

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TABLE A30.—*Experiments concerning the effect of nicotine and smoking upon the peripheral vascular system (cont.)*

Author, year, country, reference	Number and type of population	Experimental conditions[1]	Whole blood clotting time	Prothrombin time	Partial thromboplastin time	Recalcified plasma clotting time	Platelet adhesiveness	Platelet count	Platelet survival	Platelet turnover	Other	Comments
Glynn et al., 1966, Canada (71).	88 male and 17 female smokers and 8 male and 31 female nonsmokers 17–76 years of age.	3 cigarettes in 30 minutes.					(–)				*Platelet serotonin* (–) *Platelet adenosine nucleotide* (–)	Smokers found to have a greater tendency for platelet aggregation than nonsmokers.
Engelberg and Futterman, 1967, U.S.A. (59).	84 male and 63 female patients and medical house staff.	1 cigarette in 6 minutes.									*Thrombus formation time* (+) decrease	No relation found with increase in free fatty acids.
Murphy, 1968, U.S.A. (140).	Literature review with summary of data and conclusions.						(±) increase	(±) increase	(+) decrease		*Platelet adherence to vascular endothelium* (+) increase *Fibrinolysis* –(±) decrease *Thrombus formation time* (+) decrease	

Symbols:
– = No effect.
± = Questionable effect.
+ = Definite effect.

[1] Results, unless otherwise stated, concern specific coagulation test as measured before and after smoking procedure noted.

TABLE A30.—*Experiments concerning the effect of nicotine and smoking upon the peripheral vascular system*

Author, year, country, reference	
Meyer and Maddock, 1940, U.S.A. (124).	20 subjects (including heavy smokers) were studied for the effects of the following procedures on skin temperature: the inhalation of a lit cigarette, inhalation through an empty paper tube, or the administration of 1 mg. nicotine intravenously. All subjects responded with decreased cutaneous temperature following the smoking and nicotine procedures. No changes were noted following sham smoking.
Mullins and Shulman, 1940, U.S.A. (138).	A number of experimental groups, each consisting of 5–11 persons, were studied for the effects of deep breathing and cigarette smoking on skin temperature and digit or limb plethysmography. The authors concluded that deep breathing alone could account for the changes in temperature and blood flow noted upon smoking and noted that denicotinized cigarettes evoked the same or greater vasoconstriction as that noted following the smoking of a standard cigarette.
Shepherd, 1951, Ireland (173).	10 young male smokers were studied with plethysmography before and after the normal and rapid inhalation of a standard cigarette. The author noted that rapid inhalation was associated with a prolonged decrease in extremity blood flow while a more natural rate of inhalation was followed by a momentary decrease in flow. The author considered the former reaction to represent the pharmacologic effect of the smoke and the latter to represent the physiologic response to deep breathing, as the natural inhalation of an café cigarette produced the same transient decrease in flow as did the natural inhalation of the lit cigarette.
Friedell, 1953, U.S.A. (70).	52 male and 45 female young smokers and nonsmokers were studied for the effects of smoking on hand blood volume as measured by the use of radioactive iodinated albumin. The inhalation of unfiltered cigarettes was associated with an average decrease in hand blood volume of 19 percent in men and 33 percent in women; while filtered cigarettes showed respective decreases of 11 percent and 21 percent.
Strömblad, 1959, Sweden (181).	11 male and female subjects (smokers and nonsmokers) were studied for the effect of the intra-arterial administration of nicotine (brachial artery) on blood flow to the hand as measured by venous occlusion plethysmography. Increasing doses of nicotine were associated with increasing numbers of individuals manifesting vasoconstriction. The vasoconstrictive effects of nicotine were abolished by the prior administration of either hexamethonium or pentolinium.
Barnett and Boake 1960 Australia (12).	8 male patients with intermittent claudication (7 were heavy smokers) were studied for the effect of smoking on blood flow to the leg as measured by venous occlusion plethysmography. Smoking an unfiltered cigarette was found not to produce any consistent changes in blood flow to the calf or foot of the affected leg.
Freund and Ward, 1960, U.S.A. (68).	15 male prison inmates (less than 35 years of age) and 14 male patients with peripheral vascular disease (approximately 65 years of age) were studied for the effect of smoking on digital circulation as measured by skin temperature, plethysmography, and radioisotope clearance from the skin. Smoking was found to adversely affect the first and third measures in a significant manner (while plethysmographic values were variable) only in the healthy prisoners and not of all in the patient group.
Roth and Schick, 1960, U.S.A. (161).	100 normal individuals underwent 425 experimental procedures concerning the effect of smoking on the peripheral circulation. Smoking was found to be associated with a decrease in extremity skin temperature.

(71) GLYNN, M. F., MUSTARD, J. F., BUCHANAN, M. R., MURPHY, E. A. Cigarette smoking and platelet aggregation. Canadian Medical Association Journal 95(11): 549–553, September 10, 1966.

(59) ENGELBERG, H., FUTTERMAN, M. Cigarette smoking and thrombotic coagulation of human blood. Arenives of Environmental Health 14(2): 256–270, February 1967.

(124) MOYER, C. A., MADDOCK, W. G. Peripheral vasospasm from tobacco. A.M.A. Archives of Surgery 49(2): 277–285, February 1940.

(138) MULINOS, M. G., SHULMAN, I. The effects of cigarette smoking and deep breathing on the peripheral vascular system. Studied by five methods. American Journal of the Medical Sciences 199(5): 708–720, May 1940.

(173) SHEPHERD, J. T. Effect of cigarette-smoking on blood flow through the hand. British Medical Journal 2: 1007–1010, October 27, 1951.

(70) FRIEDELL, M. T. Effect of cigarette smoke on the peripheral vascular system. Radioactive iodinated albumin used as indicator of volumetric change. Journal of the American Medical Association 152(10): 897–900, July 4, 1953.

(13) BARNETT, A. J., BOAKE, W. C. Cigarette smoking and occlusive arterial disease of the legs. Medical Journal of Australia 1: 240–242, February 13, 1960.

(161) ROTH, G. M., SCHICK, R. M. The effects of smoking on the peripheral circulation. Diseases of the Chest 37(2): 203–210, February 1960.

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TABLE A30.—*Experiments concerning the effect of nicotine and smoking upon the peripheral vascular system (cont.)*

Author, year, country, reference	
Bustamante et al., 1960, U.S.A. (168).	8 males (18–31 years of age) were studied for the effect of intravenous nicotine on extremity temperature and blood flow. Intravenous nicotine was found to evoke a decrease in skin temperature while increasing muscle blood flow. The former effect began sooner and lasted longer than the latter.
Auerbach and Roth, 1969, U.S.A. (8).	30 healthy individuals (19–59 years of age) were studied for the effect of smoking two cigarettes on extremity pulse volumes and skin temperatures. Smoking was found to be associated with a 2–4 percent decrease in skin temperature and a 45–50 percent decrease in blood pulse volumes in segments of the finger, calf, and toe.

(162) ROTTENSTEIN, H., PRINCE, G., RUSS, E., FELDER, D., MONTGOMERY, H. Influence of nicotine on the blood flow of resting skeletal muscle and of the digits in normal subjects. Annals of the New York Academy of Sciences 90(1): 102–113, September 27, 1960.

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1972 Page 460

The Health Consequences of Smoking

A Report of the Surgeon General: 1972

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
Health Services and Mental Health Administration

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INTRODUCTION

In the United States more people die from coronary heart disease (CHD) than from any other disease; furthermore, CHD is the single most important cause of excess death among cigarette smokers (54, 57). The 1971 report, "The Health Consequences of Smoking" (56), outlined the growing magnitude of this problem and summarized the relationship between smoking and coronary heart disease as follows:

1. Data from numerous prospective and retrospective studies confirm the judgment that cigarette smoking is a significant risk factor contributing to the development of coronary heart disease including fatal CHD and its most severe expression, sudden and unexpected death. The risk of CHD incurred by smokers of pipes and cigars is appreciably less than that by cigarette smokers.
2. Analysis of other factors associated with CHD (high serum cholesterol, high blood pressure, and physical inactivity) shows that cigarette smoking operates independently of these other factors and can act jointly with certain of them to increase the risk of CHD appreciably.
3. There is evidence that cigarette smoking may accelerate the pathophysiological changes of pre-existing coronary heart disease and therefore contributes to sudden death from CHD.
4. Autopsy studies suggest that cigarette smoking is associated with a significant increase in atherosclerosis of the aorta and coronary arteries.
5. The cessation of smoking is associated with a decreased risk of death from CHD.
6. Experimental studies in animals and humans suggest that cigarette smoking may contribute to the development of CHD and/or its manifestations by one or more of the following mechanisms:
   a. Cigarette smoking, by contributing to the release of catecholamines, causes increased myocardial wall tension, contraction velocity, and heart rate, and thereby increases the work of the heart and the myocardial demand for oxygen and other nutrients.
   b. Among individuals with coronary atherosclerosis, cigarette smoking appears to create an imbalance between the increased needs of the myocardium and an insufficient increase in coronary blood flow and oxygenation.
   c. Carboxyhemoglobin, formed from the inhaled carbon monoxide, diminishes the availability of oxygen to the myocardium and may also contribute to the development of atherosclerosis.
   d. The impairment of pulmonary function caused by cigarette smoking may contribute to arterial hypoxemia, thus reducing the amount of oxygen available to the myocardium.
   e. Cigarette smoking may cause an increase in platelet adhesiveness which might contribute to acute thrombus formation.

Recent epidemiological, pathological, and experimental studies add to the understanding of the relationship between smoking and CHD. These studies point to cigarette smoking as one of the major risk factors leading to CHD and help clarify some of the biomechanisms through which this occurs.

(54) U.S. PUBLIC HEALTH SERVICE. The Health Consequences of Smoking: A Public Health Service Review: 1967. Washington, U. S. Department of Health, Education, and Welfare, Public Health Service Publication No. 1696, 1967. 199 pp.

(57) U.S. PUBLIC HEALTH SERVICE. Smoking and Health. Report of the Advisory Committee to the Surgeon General of the Public Health Service. Washington, U.S. Department of Health, Education, and Welfare, Public Health Service Publication No. 1103, 1964. 387 pp.

(56) U.S. PUBLIC HEALTH SERVICE. The Health Consequences of Smoking: A Report of the Surgeon General: 1971. Washington, U.S. Department of Health, Education, and Welfare, DHEW Publication No. (HSM) 71-7513, 1971. 458 pp.

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Acceptance of Morbidity Statistics. In 1971, Sterling published an article in the Journal of the American Statistical Association (66: 251-257), analyzing the statistics used in the earlier documents. The article is reproduced in its entirety.

A Review of the Claim that Excess Morbidity and Disability Can Be Ascribed to Smoking

THEODOR D. STERLING*

This article analyzes an HEW report on smoking and morbidity based on a study suffering from two major flaws. First, the data actually presented in the report may not warrant the conclusion that cigarette smoking leads to increases in disease and disabilities (female smokers, by and large, report fewer diseases than do female non-smokers, and moderate smokers, comprising over 72% of the smoking population for males and over 88% for females, report the fewest number of diseases and have the lowest prevalence rates for both men and women); second, inadequate attention has been paid to the potential influence of various aspects of the survey method on these findings. There appears to be several obvious sources of error for which adjustments were not made.

1. INTRODUCTION

In 1967 the U. S. Department of Health, Education, and Welfare published a report entitled *Cigarette Smoking and Health Characteristics* which offers

> . . . statistics . . . on selected health characteristics and cigarette smoking habits of the civilian, noninstitutional population 17 years and over in the United States during the period July 1964–June 1965 [10, title page].

The report is careful *not* to claim that it establishes a relationship between smoking and chronic and acute illnesses and disabilities. However, it has become the basis for a number of claims that smoking causes a large variety of illnesses and disabilities. These claims are summarized in an official report by HEW which makes specific claims about the total days Americans are supposed to have lost from work or spent at home "because cigarette smokers have higher disability rates than non-smokers" [22]. These figures are large—77 million days lost from work, 88 million days spent in bed, 396 million days of restricted activity. While none of these figures even appear in the original study (they are estimates said to be based on figures contained in that study although the estimating procedures are nowhere published), the same figures are also used widely and continuously in pamphlets circulated by the National Clearinghouse for Smoking and Health and are repeated in a recent information publication prepared by a private contractor [5]. Yet, the data provided by the National Center are extremely ambiguous. (With clever manipulation, they could be made to support the contention that smoking is even beneficial to health.)

Specifically, the study on cigarette smoking and morbidity suffers from two major flaws:

1. The data actually presented in *Cigarette Smoking and Health Characteristics* may not, in fact, warrant the conclusion that cigarette smoking leads to increases in disease and disabilities:
   a. Female smokers, taken as a group, by and large report fewer diseases and disabilities and their prevalence rates, computed on the basis of these reports, are generally smaller than those for non-smokers.
   b. Moderate smokers (those who consume less than a half or less than a full pack a day) very often report the fewest number of diseases and have the lowest prevalence rates for both men and women. If the conclusions of the report hold, they do so for heavier smokers only who comprise considerably less than half the sample of smokers.
2. Inadequate attention has been paid to the potential influences of various aspects of the survey methods on the findings. Specifically, there appear to be a number of obvious sources of bias and error for which adjustments were not made.

The sampling plan of the National Health Survey follows a multi-stage design which permits a continuous sampling of the civilian population of the United States. The first stage of this design consists of drawing a sample of 357 from about 1,900 geographically-defined Primary Sampling Units into which the United States has been divided. The PSU is a county, a group of contiguous counties, or a standard metropolitan statistical area. Within PSUs, ultimate stage units, called segments, are defined in such a manner that each segment contains an expected 900 households. Each week a sample of about 90 segments is drawn. Household members in the approxi-

* Theodor D. Sterling is professor, Department of Applied Mathematics and Computer Science, Washington University, St. Louis, Mo. This article is based on three studies conducted by the author over a two-year period on the validity of recent claims about the effects of smoking on health. The results of these studies were immediately made available to the National Center for Health Statistics, the National Institutes of Health, the cigarette industry, and other interested and appropriate agencies and individuals. In substance this article is based on the author's testimony on April 29, 1969, to the Interstate and Foreign Commerce Committee of the House of Representatives, Representative Harley O. Staggers, Chairman.

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mate 800 of the households in the segments are interviewed concerning factors related to health. Since it would be impossible to interview each person residing in the household, the information about all residents in a household is obtained from adults over 19 who are present when the interviewer calls. These are usually the women homemakers, elderly or retired persons, or ill or unemployed members of the household. Thus, the information is partially collected by direct interview and partially by "proxies." In some five to ten percent of the sample households no interview is obtained for one or another reason. The problem created by this "missing information" is handled in various ways, but whatever procedure is followed it ultimately contributes as an additional source of variability and potential bias.

2. DO THE DATA ACTUALLY SHOW AN ASSOCIATION BETWEEN SMOKING AND DISEASE AND DISABILITY?

Several studies that demonstrated the effect of smoking on health have been criticized sharply because of their methods of obtaining data and of analyzing them. The attitude of these critical evaluations was that since the method of investigation was seriously impaired, the purported findings of the study did not need specific refutation. However, such an assumption may be unfounded, and, indeed, may be a disservice. These attempted refutations gained no strength from the fact that they were advanced by notable statisticians; the truth is that neither to the average physician nor to the man in the street does the name of Berkson or of Sir Ronald Fisher mean any more than Tom, Dick, or Harry. Thus, even when an investigation does not appear to provide a foundation on which to base statistical inference, it is still necessary to examine the data to see whether or not there exists an observed difference between smokers and nonsmokers on which any claims may be based. Besides, such a comparison may prove to be interesting.

2.1 The Female Enigma

Responses by women are based predominantly on self interviews (83 percent) as compared to men, of whom only 40 percent were self interviewed. Since it is known that self interviews are much more accurate than proxy responses [1, 13, 14, 17, 18], a comparison between reported diseases among female smokers and non-smokers would appear to be a much more accurate contrast than the corresponding comparison among males. Yet, the percentage of female non-smokers 17 years of age and over who reported one or more chronic conditions is consistently smaller than that of female smokers. Since there were considerable differences in age distributions between smokers and non-smokers, the data were adjusted to a new base using an indirect method. (We shall discuss the age adjustment method used in a moment and just note now that when this indirect age adjustment is done, the difference between smokers and nonsmokers, especially for males, is often reversed.) However, even if we accept for the moment the age adjustment method, the comparisons between disease rates for chronic conditions between smokers and non-smokers are far from clear. Table 1 shows prevalence rates for females 17 years and over, both unadjusted and adjusted by the indirect method. We see that for heart conditions, hypertension, and hearing impairment the age-adjusted rates remain lower for smokers than for non-smokers. Certainly an inspection of this table, regardless of whether or not we accept the indirect age adjustment method, does not unambiguously lead us to ascribe more disease to smokers.

Table 1. PREVALENCE RATES OF CHRONIC CONDITIONS PER 100 FEMALES 17 YEARS AND OVER IN NHS, BY CIGARETTE SMOKING STATUS

Selected chronic condition	Unadjusted for age[a]			Adjusted for age[b]		
	Total population	Persons who never smoked	Persons who ever smoked	Total population	Persons who never smoked	Persons who ever smoked
Heart condition (excluding rheumatic heart disease)	4.3	5.5	2.6	4.2	4.5	3.9
Arteriosclerotic heart disease, including coronary disease (subcategory of heart conditions)	0.7	0.8	0.6	—[c]	—[c]	—[c]
Hypertension without heart involvement	8.3	10.1	5.8	8.2	8.6	7.4
Chronic bronchitis and/or emphysema	2.0	1.3	3.1	2.0	1.2	3.4
Chronic sinusitis	12.2	11.1	13.9	12.2	11.1	14.0
Peptic ulcer	1.9	1.6	2.5	1.9	1.6	2.6
Arthritis	13.0	15.4	9.7	12.9	12.9	12.8
Hearing impairment	5.7	7.1	3.9	5.6	5.8	5.4
All other chronic conditions	100.8	101.0	98.0	100.1	95.9	107.8
All chronic conditions	149.0	155.9	139.7	147.8	142.2	158.6

[a] *Source:* [16, Table 6, pp. 32–3].
[b] *Source:* [16, Tables 7–17, pp. 34–42].
[c] Not given.

2.2 The Enigma of the Moderate Smoker

Most reports about smoking effects pay close attention to individuals who fall into "heavy" smoking categories. The fact that heavy smokers usually report more diseases than do more moderate smokers is implicitly taken as a function of "dose." However, there are several problems with emphasizing the fate of heavy smokers, of which two deserve special attention:

1. The majority of smokers use cigarettes in moderate amounts [5, 7]. They may report as few or fewer diseases than do non-smokers (as is the case in this report).
2. Heavy smokers are relatively few in number and it is known that they also tend to be heavy drinkers [6], over-eaters (usually inferred from heavier weight of smokers or higher serum cholesterol levels, or both [2, 4, 9, 10, 19]), under-exercisers [21, Table 18], and are perhaps careless about other vices that may detract from their health. It is unclear to what extent these other factors contribute to the observed diseases.

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It is thus not sufficient to report an increase in disease among heavy smokers without clarifying if smoking *in any amount* results in an increase in disease.

What is "moderate" or "excessive" smoking is difficult to define. We have taken a reported smoking rate of one half pack or less as moderate but include also the group reporting a smoking rate of one half to a full pack a day. In so doing, we clearly deal with the majority of smokers, so that observations on them ought to receive proper attention. After all, no fewer than 72.6 percent of the males and 88.5 percent of the female smokers reported that they smoked a pack or less a day presently. Although these percentages decline somewhat if smokers are grouped by heaviest amount smoked daily, those who smoke less than one pack a day make up the overwhelming majority of the smoking population. (Relevant figures are summarized in [16, Table 3, pp. 27–8].)

The report stresses that rates of most diseases and disabilities increase with increases in the number of cigarettes smoked. In a way, this is correct. There is this parallel increase in disease and smoking. The trouble is that, as often as not, non-smokers report disease rates that are greater than those reported by smokers who consume less than a half or full pack a day. Table 2 compares observed prevalence rates and prevalence rates adjusted for peculiarities and difference in age distribution between moderate smokers and non-smokers. Moderate smokers, whether male or female, tend to report less disease than do non-smokers. Similar observations are true for reports of disabling confinements. The number of disease categories for which moderate smokers report a smaller prevalence differ for adjusted and unadjusted prevalence rates. Of those who smoke one half pack or less, males reported fewer diseases in six out of seven disease categories (adjusted or unadjusted) and females reported fewer diseases in six out of eight. For smokers who consume between a half and a full pack a day, males reported fewer diseases in six out of eight disease categories and females in five out of eight (for unadjusted) and three out of eight (for adjusted prevalence rates).

Table 2. ESTIMATED UNADJUSTED AND AGE-ADJUSTED PREVALENCE RATES FOR DIFFERENT CHRONIC CONDITIONS FOR 100 MODERATE- AND NON-SMOKING MALES AND FEMALES[a]

Condition, by sex	Unadjusted			Age-adjusted		
	Never smoked	Half pack or less[b]	Half to full pack[b]	Never smoked	Half pack or less[b]	Half to full pack[b]
Heart condition (excluding chronic rheumatic heart disease)						
Males	4.6	3.2	3.4	4.1	3.8	4.4
Females	5.5	2.0	2.2	4.3	2.6	3.5
Hypertension						
Males	4.4	3.4	3.1	4.1	3.8	3.6
Females	10.1	6.0	5.0	8.6	7.4	6.5
Chronic bronchitis						
Males	1.0	-	2.1	1.0	-	2.3
Females	1.3	1.4	3.4	1.2	1.6	4.0
Chronic sinusitis						
Males	8.2	7.6	10.1	8.3	7.7	10.1
Females	11.1	10.7	13.9	11.1	10.8	14.0
Peptic ulcer						
Males	2.3	2.9	4.6	2.4	3.0	4.6
Females	1.0	1.9	2.4	1.6	2.0	2.5
Arthritis						
Males	7.3	5.5	5.0	6.8	6.6	5.9
Females	15.4	8.7	9.1	12.9	11.1	12.5
Hearing impairment						
Males	8.9	6.9	6.2	8.0	7.0	7.5
Females	7.1	3.2	3.7	5.8	4.2	5.3
11 other chronic conditions						
Males	74.8	62.7	69.8	72.5	65.4	73.0
Females	103.0	78.5	89.4	95.9	85.1	99.5

[a] *Source:* [16, Tables 9–15, pp. 35–42].
[b] By heaviest amount smoked.

Of course, the non-smoker category may include a certain number of persons who do not smoke because of chronic illness. Yet, there is no substantive evidence offered that this is so or that moderate smoking is not prevalent among individuals who are ill from a number of causes. On the other hand, we cannot explain the higher prevalence of morbidity among non-smokers because a certain number of the very ill smokers may have been urged or forced to join the non-smokers. We purposely selected persons who never smoked to compare with moderate smokers. In short, while the peculiarities in the relationship between the amount smoked and the number of diseases reported make it difficult in the extreme to explore and explain these data, it is not easy to see what purpose could be served by hiding this pertinent result by a blanket statement that the increase in disease appears to be related to the amount smoked.

3. WHAT WERE THE POTENTIAL INFLUENCES OF THE SURVEY METHODS ON THE FINDINGS?

The National Center for Health Statistics has been in the forefront of developing and investigating probability sampling methods, attendant survey methodology, and sources of error and ways to adjust for them. For this reason, it is not easy to understand why so many potential sources of bias were simply ignored. This is doubly surprising because the basic methodological investigations that have shown only a small correlation between the incidence of medically-documented disabilities and the estimated number of these same diseases derived from questionnaire interview methods come from two widely-known and well-respected studies sponsored by and published through the NCHS. These detailed studies had shown that proxy responses tend to suffer from errors roughly twice the size of those which result from self respondents [13, 14]. One of these studies is especially relevant because it demonstrated that "psychological" or "sociological" factors have profound effects on the size of errors in responses of proxies, much more so than on responses that came from self respondents [14].

An interview technique which obtains data about a larger population by interviewing those members of a household who are fortuitously present when the interviewer calls was, in fact, recognized during the inception of the National Health Survey as a serious source of error and the budgetary limitations forcing this procedure upon

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the survey properly lamented [11, 12]. Yet, national estimates on the effect of smoking are based on these same data, with the fond hope that errors in them are randomly distributed throughout all categories of information so that estimates of different categories (such as for smokers and non-smokers) are not affected differentially.[1] Given the public nature of debate on smoking and health in the press and on television, there is surely a good possibility that proxy respondents may be affected by opinions and beliefs concerning smoking and, accordingly, color their answers to interviewers. Similar problems exist for such obvious potential sources of bias as employment or non-employment or for other "characteristics" of respondents.

3.1 The Smoking-Proxy Bias

The survey obtained records for 41,745 males. Of these, 29,322 were reported to be smokers. Only 12,440 smoking males reported directly about their disease and disabilities. Of the smoking males for whom information was obtained by proxy, the largest group had information obtained from their spouse. Counting only wives who either smoked or did not at the time of the interview, there were 11,440 such male smokers, comprising approximately 40 percent of the sample of male smokers. It may be reasonable to suppose that among non-smoking informants (mostly wives) there are those who do not smoke because of the belief that smoking could be harmful. By comparing the number of diseases reported for smokers by informants who do smoke and informants who do not smoke, we can isolate to some extent the effect of the belief (that may be held consciously or not) that smoking is harmful in terms of the number of diseases each group reports for their smoking husband.

The 11,440 male smokers were divided into the 5,678 proxies whose wives had never smoked and the 5,562 proxies whose wives smoked at the time of interview. The percentage of smoking males for whom one or more chronic conditions were reported by the wife, the percentage for whom different kinds of chronic conditions were reported, and the average number of chronic conditions reported for each proxy for whom diseases were reported are shown in Table 3. As can be seen, non-smoking wives uniformly reported more disease for their smoking husbands than did the wives who themselves did smoke. But not only were more individuals reported as having disease by non-smoking than by smoking wives, but the number of diseases reported for each husband was also affected by whether or not the wife smoked.

The comparison of the number of diseases reported by smoking and non-smoking informants is of special significance for the category of bronchitis/emphysema. Since smokers often cough, the question may be raised to what extent this cough is perceived by non-smokers as a sign of disease while it may be largely ignored by smokers as a simple response to irritation. Certainly it would be unreasonable to suppose that the wife's failure to smoke causes an increase in the number of instances of husbands with bronchitis and emphysema (or of any other chronic disease).

Table 3. PERCENT OF PROXY SMOKING MALES FOR WHOM CHRONIC CONDITIONS, RESTRICTED ACTIVITY, CONFINEMENT TO BED, AND LOST DAYS OF WORK WERE REPORTED BY SMOKING AND NON-SMOKING WIVES[a]

Condition	Wife does not smoke	Wife smokes
One or more chronic conditions	57.7%	56.0%
Heart disease	3.10	3.00
Hypertension	3.65	3.16
Bronchitis/emphysema	2.10	1.75
Chronic sinusitis	11.10	11.03
Peptic ulcers	4.75	4.72
Prevalence of restricted days because of illness:		
Restricted activity days during last two weeks	7.90	7.49
Days spent in bed during last year	12.48	12.11
Days lost from work during last two weeks	4.61	3.83
Average number of all chronic conditions reported	1.94	1.77
Average number of restricted days because of illness:		
Average restricted activity days during last two weeks	5.65	5.54
Average days spent in bed during last year	24.46	19.16
Average days lost from work during last two weeks	5.80	4.00

[a] From data supplied by the National Center for Health Statistics.

Very much the same picture emerges when we compare the number of restricted activity days, days spent in bed, and days lost from work and the average number of such lost days reported by wives who smoke with the number reported by wives who do not smoke. The percentage of males for whom it is reported that they have lost days is uniformly smaller if the wife reporting these disabilities does smoke than if the wife does not. The same is true for average number of days reported with the exception of work-loss days where smoking wives report more work days lost than nonsmoking wives.

Since the difference in the raw prevalence of reported diseases and disabilities as described in [16] is often no larger and sometimes even smaller than the prevalence in reported disease and disabilities between smoking and non-smoking proxy informants, it is not impossible that the observed difference in prevalence between smokers and non-smokers may have been due to these psychological factors. In any case, it seems a pity that the proper adjustment for this factor was not included in the analysis of the NCHS data.

[1] Personal communication from Mr. Theodore D. Woolsey, the Director of NCHS.

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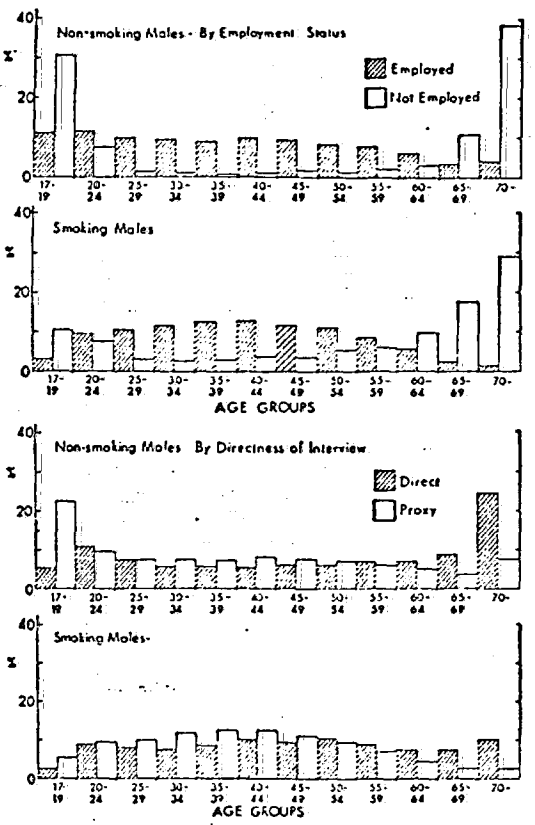
3.2 The Adequacy of Age Adjustment Methods

There are several methods of comparing two sets of rates when large confounding effects may differentially distort them. One of the obvious confounding effects in comparing disease rates is age. Disease rates are obviously related to age, with the highest rates occurring among the very young and the aged. If the age distribution for smokers and non-smokers were similar, then rates of disease among them could be compared directly. However, the age distributions of sampled smokers and non-smokers were quite different. Thus, observed differences in disease rates between smokers and non-smokers may be related to differences in their age distributions rather than to the fact that they differ in smoking habits. The data in the report *Cigarette Smoking and Health Characteristics* were adjusted, therefore, for peculiarities of their age distribution. There are, however, two objections to the analyses in the report.

Adjustments do not go far enough. There are a number of differences between smokers and non-smokers other than age and sex that need to be considered. Observed differences in rates between smokers and non-smokers may be related to differences between the two groups on such factors as employment status, directness of interview, characteristics of proxy informants, and so on. Secondly, the indirect method of age adjustment used in the report is most easily affected by extraneous factors and ought not to have been used.

The figure gives some idea of the differences between male smokers and non-smokers on employment status and directness of interview by age. (The distributions are as markedly different for females, but not shown here.) Although we cannot simultaneously adjust for all these factors from the data at hand, some indication of the effect of the employed-unemployed dimension on reports of diseases and disabilities may be inferred from Table 4. The effect of differences in age distributions by employment status or directness of interview on number of reported diseases may well mask a much more profound effect due to smoking or, quite to the contrary, cause such an effect to appear when none actually exists. Considering the profound differences in age distribution existing between employed and unemployed members of the sample or between direct and proxy respondents, it is difficult to judge what indirect age adjustment actually accomplished. It would have been more appropriate under the circumstances to use a direct age adjustment method or compare age-specific disability rates. (All other reports on the same data published by NCHS do report more detailed age-specific rates or use a direct method of age adjustment that reflects age-specific rates more directly than the indirect method of age adjustment used only in this report and no other. This report does present age-specific data, but for large age ranges as 17 to 44, 45 to 64, and over 65 years, which is really not of much help.) Detailed age-specific rates then should have been shown and adjusted for influences on responses due to employment and proxy status at the very least.

AGE DISTRIBUTION OF MALES—BY EMPLOYMENT STATUS AND BY DIRECTNESS OF INTERVIEW[a]



[a] From data supplied by the National Center for Health Statistics.

3.3 How Many Smokers Are There?

The prevalence of smoking in the NHS sample is of prime importance since, after all, smoking is the independent variable in the comparison. Yet, nowhere do we find an attempt to assess the accuracy with which numbers of smokers or non-smokers were obtained. There are two well-known studies available that make comparable observations of the distribution of smoking in the U. S. population. It is interesting that both differ quite emphatically from the age distribution of smokers and non-smokers obtained from the household interview [5, 7]. These differences are summarized in Table 5. Again, the difference is much larger and much more pronounced among males than females, most likely because there were many more proxies among the former.

These data need not indicate that the NCHS survey was plagued by exceptionally large errors in counting smokers and non-smokers. After all, the error may have been in Hammond's or Hearn-zel's studies. However, it is

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Table 4. PERCENT OF SAMPLE POPULATION EXPERIENCING DISABILITIES, BY EMPLOYED AND UNEMPLOYED[a]

Employment status	Bed confinement last two weeks	Bed confinement last year	Restricted activity last two weeks	Short Hospital stay last year	One or more chronic conditions	Three or more chronic conditions
			Males			
Employed	3.8	11.0	7.7	7.7	54.2	11.5
Unemployed	7.9	19.5	30.3	12.8	69.9	30.6
			Females			
Employed	5.7	13.9	10.0	11.3	55.8	14.9
Unemployed	8.1	18.0	15.4	18.6	66.0	25.5

[a] From data supplied by the National Center for Health Statistics.

clear that even for such a simple question as whether an individual has ever smoked, large errors appear if a data gathering procedure relies heavily on proxies. Again, it would have been important for the credibility of the study if more attention had been given to the accuracy of smoking histories and discrepancies between the survey's results and that of other studies examined.

4. CONCLUSIONS

Surely it is important to know to what extent smoking harms the population of this country. It may be even that given existing budget limitations, better methods of inquiry than a household sampling survey may not be available. Yet, it hardly helps to clarify this problem if data resulting from methods that are known to produce

Table 5. COMPARISON OF NON-SMOKERS' AGE DISTRIBUTION[a]

Sex and age group	Number of non-smokers from NHS [a]	Number of non-smokers expected according to Heanszel, et al. [b]	Percent difference between observed and expected for Heanszel, et al.	Number of non-smokers expected according to Hammond [c]	Percent difference between observed and expected for Hammond
Males					
18-24	4,396	3,721	15%	--[d]	--[d]
25-44	4,926	4,734	4	--[d]	--[d]
45-64	4,406	5,274	20	5,483	24%
65+	3,299	4,376	33	3,913	18
Females					
18-24	6,765	6,691	1	--[d]	--[d]
25-44	11,019	12,740	16	--[d]	--[d]
45-64	11,723	14,490	23	13,259	12
65+	8,250	8,756	6	8,666	5

[a] As obtained from household interviews with the expected number of non-smokers based on two studies of tobacco smoking patterns of the U.S. population.
[a] *Source:* [10, Table 1, pp. 23–4].
[b] *Source:* [7].
[c] *Source:* [5].
[d] Not given.

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large errors and are possible sources of bias are subjected to inadequate and perhaps inappropriate analyses and not enough attention is paid to the potential influences of various aspects of the survey methods on these findings. Perhaps if any lesson is to be learned from this issue, it is not that smoking causes untold diseases and disabilities and loss from work, but that claims about such controversial topics need to be carefully and intelligently reviewed, even if they are made by public agencies or by other generally reliable sources.

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A prospective study of 973 men born in 1913 in Göteborg, Sweden, was undertaken in 1963 (*51, 52*). The proportion of myocardial infarctions among cigarette smokers was significantly greater than among nonsmokers ($P < .05$), and the incidence of myocardial infarction rose with increasing cigarette consumption (table 1). Of the 35 individuals who experienced a myocardial infarction between 1963 and 1970, only two had been nonsmokers; in the whole population of men born in 1913, 56 percent were smokers.

Although angina pectoris was more common in smokers than nonsmokers, the difference was smaller than for myocardial infarction and was not statistically significant (*52*).

Paffenbarger, et al. (*42*) reported on the health experience of 3,263 longshoremen studied over the past 18 years. During this interval 1,698 were known to have died, 350 dying from CHD. Longshoremen who smoked more than 20 cigarettes a day faced a risk of coronary death which was more than twice as great as that of the group made up of both nonsmokers and smokers of less than 20 cigarettes a day ($P < .01$).

Keys, et al. (*30*) analyzed the 20-year CHD incidence among 279 Minnesota men aged 47 through 57 years who were CHD free at entry into the study. The relationship of cigarette smoking habits at the start of the study to the subsequent incidence of CHD was examined. The originally published table of results was incorrect and the authors have supplied a corrected table which appeared in a later issue of the same journal (table 2). The morbidity ratio for "hard CHD" (CHD deaths plus myocardial infarctions not resulting in death) among those smoking more than 10 cigarettes a day is similar to that reported from the large prospective studies. However, with the small number of cases in each smoking category, there are no statistically significant differences in the incidence of CHD between the categories, either singly or combined.

Retrospective studies of CHD have recently been reported from Czechoslovakia, Sweden, Norway, and India which corroborate earlier studies linking cigarette smoking with excess CHD morbidity and mortality.

TABLE 1.—*Incidence (1963–1970) of heart infarct in relation to tobacco consumption in "The Men Born in 1913," Göteborg, Sweden.*

n = 855

Smoking classification	Heart infarct Number	Heart infarct Percent
Never smoked n = 207	(2)	1.0
Stopped smoking n = 168	(2)	1.0
Cigarette smokers	(13)	6.0
1–14 cig/day n = 234		
15–24 cig/day n = 138	(9)	7.0
≧25 cig/day n = 33	(4)	12.0
Pipe/cigar n = 75	(5)	7.0

SOURCE: Tibblin, G., Wilhelmsen, L. (51).

TABLE 2.—*Cigarette smoking at entry and subsequent 20-year CHD incidence among Minnesota men.*[1]

Age	Number of men	Item	Never	Smoking habit (cigarettes/day) Stopped	<10	10–19	>20
47,48	53	% with habit	23	19	9	19	30
49,50	51	% with habit	33	20	14	10	23
51,52	69	% with habit	33	26	14	14	13
53,54	53	% with habit	36	30	8	13	13
55–57	51	% with habit	24	33	8	18	17
47–57	277	Number of men	83	71	30	41	52
47–57	277	Hard CHD rate (%)	12.0	15.5	10.0	17.1	21.2
47–57	277	Hard CHD rate (SE)	± 3.6	± 4.3	± 5.5	± 5.9	± 5.7
47–57	277	Hard CHD Morbidity Ratio	1.00	1.29	.83	1.43	1.77
47–57	277	All CHD rate (%)	±21.7	±21.1	±16.7	±19.5	±26.9
47–57	277	All CHD rate (SE)	± 4.5	± 4.8	± 6.8	± 6.2	± 6.1
47–57	277	All CHD Morbidity Ratio	1.00	.97	.77	.90	1.24

[1]Cigarette smoking habits, by age at start of the 20-year follow-up, 20-year incidence rates (per 100 men), and standard errors (SE) of the rates. "Hard CHD"—CHD death and myocardial infarct. "All"—angina pectoris and other CHD diagnoses. "Deaths"—from all causes except violence.

SOURCE: Modified from Keys, A., et al. (30).

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The Prague study (19) included 443 men between the ages of 60 and 64 years. Significantly more ($P < .05$) individuals with a "probable" myocardial infarction were found among cigarette smokers than among nonsmokers or pipe and cigar smokers.

The smoking habits of 120 patients with myocardial infarction who were hospitalized in Göteborg were compared with those of the entire "men born in 1913" population sample (17, 62). A significantly ($P < .01$) greater number of smokers and heavy smokers (more than 15 cigarettes a day) were found in the myocardial infarction group than in the population sample.

The Bergen, Norway, cross sectional study of 2,117 women and 2,472 men documented a relationship between smoking and CHD in men, which was most marked in the 50 to 59 year old age group (16). No effect of smoking on the prevalence of CHD in women was demonstrable in this study, and the effect in men did not appear to be related to the daily number of cigarettes smoked.

In New Delhi, 100 "well documented" cases of ischemic heart disease were compared with an equal number of control cases (8). In this study, significantly more ($P < .01$) of the case group smoked cigarettes regularly than the control group (Morbidity Ratio = 2.1).

Mulcahy, et al. (40) recently found a positive association between coronary heart disease mortality rate and calculated per capita cigarette consumption in 21 countries. He interpreted the results as being consistent with the hypothesis that cigarette smoking is a significant risk factor in CHD mortality.

Stamler, et al. (50) found that for both men and women the 1964 CHD mortality rates in 17 developed countries were related to average annual per capita cigarette consumption.

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INTERACTION OF SMOKING AND OTHER RISK FACTORS

The Report of the Inter-Society Commission for Heart Disease Resources summarized the evidence indicating that three risk factors (hypercholesterolemia, hypertension, and cigarette smoking) are properly designated major risk factors for premature CHD (28). Other possible risk factors including obesity, physical inactivity, diabetes mellitus, elevated resting heart rate, electrocardiographic abnormalities, a positive family history of premature CHD, and psychologic and social factors have also been described (54, 55, 56).

In the study of 973 men born in 1913 in Göteborg, Sweden, several coronary risk factors including elevated serum cholesterol, elevated serum triglyceride, low physical activity at work, and smoking were found to be related to an increased risk for the development of coronary heart disease during the subsequent years of the study. Failure to find a relationship between hypertension and an increased risk of CHD may have been due to the fact that all patients with hypertension in 1963 have been under treatment since that time.

Tibblin and Wilhelmsen (52) found that as a patient accumulated more risk factors his chance of developing CHD became substantially greater. Werkö (61) reported from the same Göteborg study that patients who were smokers, had sedentary jobs, and had both elevated cholesterol and triglycerides experienced a 4-year incidence of new coronary events of about 20 percent; the 4-year incidence among those who exhibited only one or two risk factors was much lower, ranging from 0 to 3 percent. ECG changes and anginal pain were included in the definition of new coronary events.

Paffenbarger, et al. (42) evaluated coronary risk factors in the study of 3,263 longshoremen. They found that, with the exception of diagnosed heart disease, smoking was the most important factor predictive of high risk for coronary mortality.

Keys, et al. (30) in the study of 270 Minnesota men, concluded that a positive cold pressor test, elevated serum cholesterol, and elevated systolic blood pressure had major predictive power for CHD death or infarction; in their analysis smoking seemed less important.

(28) Inter-Society Commission for Heart Disease Resources. Atherosclerosis Study Group. Epidemiology Study Group. Primary prevention of the atherosclerotic diseases. Circulation 42(6): A55–A95, December 1970.

(55) U.S. Public Health Service. The Health Consequences of Smoking. 1968 Supplement to the 1967 Public Health Service Review. Washington, U.S. Department of Health, Education, and Welfare, Public Health Service Publication No. 1696, 1968. 117 pp.

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Epidemiologic Studies. The study of (42) Paffenbarger et al. show more than what is stated in pages 462 and 463. The smoking data refers only to the less active shoremen. Furthermore, the group was artificially divided into high-and-low-risk groups and the mortality rate was greater for individuals who were less active than for cargo handlers. Portions of the Results and the entire Summary are as follows:

- As already shown, less active longshoremen sustained a death rate 27 per cent higher than cargo handlers. Smoking one or more packs of cigarettes per day doubled the risk of coronary death over that for smoking less or not at all. Risk among men with systolic blood pressure above mean levels exceeded that among those with lower levels by 84 per cent. An excess death rate of 23 per cent accompanied longshoremen with body weight above mean levels as compared with the rate for those less hefty. Men with diagnosed heart disease sustained a coronary death rate 168 per cent higher than that for peers without such diagnosis. (Although not shown in the figure, the corresponding excess for men with diagnosed coronary heart disease was 267 per cent.) And last, although not statistically significant, an excess death rate of 14 per cent attended men with abnormal glucose metabolism over that for those with normal glucose metabolism.

- These first-order relationships between six characteristics of high risk and coronary mortality suggest a rank order by declining strength of: diagnosed heart disease, cigarette smoking, higher blood-pressure level, less strenuous work activity, heavier weight-for-height, and abnormal glucose metabolism. Although a history of heart disease carries a higher risk-ratio for coronary death, it has less public health significance than either cigarette habit or higher blood-pressure level because of its lower prevalence.

Summary

We identified 350 decedents from coronary heart disease and 93 from stroke among 3,263 longshoremen in an 18-year follow-up after multiphasic screening examinations. Men with physically less active jobs, who expended 925 fewer calories per work day, sustained coronary death rates one-quarter higher than cargo handlers. Differences in coronary mortality were largest at younger ages and decreased steadily to disappearance at older ages.

Splitting the population into presumed high- and low-risk groups sorted out four other characteristics associated with coronary mortality: pre-existing heart disease, systolic blood pressure above mean levels, cigarette smoking of one or more packs per day, and weight-for-height above mean levels. The risk of coronary mortality accompanying each of these characteristics was greater for individuals who were less active than for cargo handlers.

Longshoremen with more sedentary jobs sustained stroke death rates similar to those of cargo handlers in the 18-year follow-up. Three other characteristics, however, identified groups at high-risk of stroke mortality: pre-existing heart disease, systolic blood pressure above mean levels, and abnormal glucose metabolism.

The association between work activity and coronary mortality, when considered with the lack of such association with stroke mortality, suggests that physical activity influences the myocardium or its function more than the atherosclerotic process.

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Cholesterol Levels. The importance of cholesterol levels in the blood mentioned in this page and in the next three pages has recently been questioned by Oster (Med Counterpoint 4: 13-27, 1972). The questions raised by the author relate to the value of epidemiologic studies in general. The article is reporduced in its entirety.

Oster K A: Prevention of atherosclerosis.

EDITOR'S NOTE: *Dr. Oster's paper takes issue with certain conclusions of the Inter-Society Commission Report that have been drawn from the Framingham Study concerning the risk of coronary heart disease. It particularly challenges the stated relative effect on risk of CHD at different levels of serum cholesterol. Some of the questioning is based on clinical experience confirmed by others (e.g., the unimportant effect on serum cholesterol levels of significant reductions in dietary cholesterol).*

Moreover, Dr. Oster casts doubt on the value of epidemiologic studies of this type and questions the mathematical underpinnings of the statistical methods employed in this case. To review such matters we have called upon a consulting mathematician to offer a critique of Dr. Oster's remarks as well as the methodology of the Framingham Study. His comments immediately follow Dr. Oster's paper.

In December 1970, The Inter-Society Commission for Heart Disease Resources, "comprised of outstanding leaders in the field of cardiovascular diseases and representatives of national professional organizations capable of making significant contributions," reported its suggestions for the prevention of atherosclerotic diseases.

Dr. Oster is Chief of Cardiology, Park City Hospital, Bridgeport, Conn. The author gratefully acknowledges the assistance of Michael A. Berger in the mathematical analysis of the statistical data in the Report. Mr. Berger, a student at the University of Bridgeport, was supported in this work by a research grant from the Greater Bridgeport Heart Association.

*"Primary Prevention of the Atherosclerotic Diseases": Report of the Inter Society Commission for Heart Disease Resources, Circulation 42 A:55, 1970

The Commission was created through a contract with Regional Medical Programs Service to help fulfill the requirements of Section 907 of Public Law 89-239, which established the Regional Medical Programs in 1965. The Commission worked under contract No. NH 69-29 with the Health, Science, and Mental Health Administration Department of the Department of Health, Education and Welfare. The funds came out of taxpayers' money.

In its introductory note to the reader, the Commission invites constructive criticism of the work of its study groups, particularly those who attempt to apply these guidelines. In the following paper such constructive criticism will be given and it will be shown that the Report of the Commission is prejudicial, based on dubious data and therefore probably deceptive. Furthermore, by thus wasting the taxpayers' money, the Report of the Commission, instead of advancing the cause of coronary heart disease prevention, channels the research funds overwhelmingly into narrow, preconceived, subjective, discredited areas of research. It thereby hinders, if it does not preclude, the development of other approaches which may provide more effective solutions of this problem, so vital to the health of the American people.

To the tune of scheduled press conferences and through recourse to the various media, the American people were advised to change their diets drastically and especially curtail the consumption of cholesterol to 300 mgs. daily from the usual 600 mgs. and reduce the intake of saturated fats to 35% from 40%. Admittingly having no proof on which to base these revolutionary recommendations that

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TABLE I

ESTIMATED RELATIVE REDUCTION IN CORONARY HEART DISEASE INCIDENCE (v) ASSOCIATED WITH RELATIVE REDUCTION IN SERUM CHOLESTEROL (u)

Relative decrease in serum cholesterol (u)	Relative decrease in coronary heart disease incidence (v)	Relative decrease in serum cholesterol (u)	Relative decrease in coronary heart disease incidence (v)
.01	.024	.26	.602
.02	.047	.27	.622
.03	.070	.28	.643
.04	.093	.29	.663
.05	.115	.30	.683
.06	.137	.31	.702
.07	.158	.32	.721
.08	.179	.33	.739
.09	.199	.34	.757
.10	.219	.35	.774
.11	.239	.36	.791
.12	.258	.37	.807
.13	.277	.38	.823
.14	.295	.39	.838
.15	.313	.40	.853
.16	.331	.41	.867
.17	.348	.42	.881
.18	.365	.43	.894
.19	.382	.44	.907
.20	.398	.45	.919
.21	.414	.46	.930
.22	.430	.47	.941
.23	.445	.48	.952
.24	.460	.49	.962
.25	.475	.50	.972

*Note: Values of v were obtained from relationship $v = 1 - (1 - u)^{2.5}$ as described in Fed. Proc. 21 (Suppl. No. 8) Part 2 June-August, 1962.

†The data illustrate the potential for prevention and the possibility of major declines in CHD mortality. For example, a reduction of just 10 percent in serum cholesterol (value of u = .10) is estimated to yield a 24 percent decrease in CHD incidence (value of v = .24).

...affect the life habits of the American people ...Rather the normal animal, dietary foods and the ...ising of livestock. The Commission presents some ...ed facts, studies, and tables to support their un...ven theories.

On page 455 of the Commission's Report we ...l Table 16, The Estimated Relative Reduction ... Coronary Heart Disease Incidence Associated ... Relative Reduction in Serum Cholesterol re...ferred as Table I of this article above. The ...evel v were obtained from the relationship ... $1 - (1 - u)^{2.5}$ described in a 1962 Com...

...ere v is the relative incidence of CHD ...and u is the relative serum cholesterol level. An ...example is given that a 10% reduction in the serum ...cholesterol level in the United States population ...(u = .10) is estimated to yield a 24% decrease in ...coronary heart disease incidence (v = .24).

Since such great importance is ascribed to this ...table and since it is utilized in two prior studies[2] ...we deemed it worthwhile to re-read Cornfield's original ...work and find out if the statements contained ...therein correspond with the table published by the ...Inter-Society Commission. In the entire study of ...Cornfield, we were unable to find the equation $v = 1 - (1 - u)^{2.5}$ but we do find equation (7), $P = .0091\left(\frac{Y_1}{100}\right)^{2.5}\left(\frac{Y_2}{100} - \frac{75}{100}\right)^{1.5}$ where Y_1 and Y_2 are serum cholesterol and systolic blood pressure respectively.

Cornfield states, "A 1% decrease in cholesterol would be associated with a 2.66% decrease in risk of coronary heart disease throughout the range of cholesterol values." In other words, it is not just limited to the levels of frank hypercholesterolemia, but also applicable to the lower values of cholesterol in the serum without exception. So, it to drive this point home by *reductio ad absurdum*, a lowering of cholesterol level from a normal of 220 mgs to 110 mgs per cent would put a theoretical person at an 81% less risk of coronary heart disease: the same as if lowering the cholesterol from 180 mgs. to 240 mgs per cent, providing that the experimental reduction of cholesterol is of the same risk condition that the Commission fails to mention.

Cornfield states in a personal letter: "My paper, 'Joint Dependence of Risks of Coronary Heart Disease on Serum Cholesterol and Systolic Blood Pressure: a Discriminant Function Analysis' Fed. Proc. 21, Suppl. No. 1, pp 58-61, July-August, 1962 states, 'If one could lower cholesterol levels by a given amount, say 15%, and if equation (7) describes not only the association between risk and cholesterol level in Framingham, but also the change in risk that would accompany an experimental alteration in serum cholesterol, then the relative risk would be .85^2.5, or a reduction of about 35%.'" Mathematical analysis reveals Cornfield's formula correct insofar as statistical significance is concerned.

Having shown the biological implausibility of the Report's Table 16, we turn to the collection of data for Cornfield's equation. We question this data which was given to him by the Framingham Study and the propriety of numbers from which

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TABLE II[3]

NEW CHD IN 6 YEARS FOLLOW-UP: ACTUAL AND EXPECTED NUMBER OF CASES AMONG MEN 40-59

Serum Cholesterol mg/100 cc.	Systolic B.P. mm Hg.	NEW CHD		Population at Risk
		Expected*	Actual	
200	Total	10.5	12	319
	<117	0.8	2	53
	117-126	1.4		66
	127-136	1.8	2	59
	137-146	2.3	1	65
	147-156	1.6	2	37
	157-166	0.7	1	13
	167-186	1.4	3	21
	187+ over	0.5	1	5
200-209	Total	5.9	2	133
	<117	0.5		21
	117-126	0.8	2	27
	127-136	1.4		34
	137-146	1.0		19
	147-156	1.9		16
	157-166	0.7		10
	167-186	0.4		5
	187+ over	0.1		1
210-219	Total	6.9	6	121
	<117	0.4		15
	117-126	0.9	1	25
	127-136	1.0	2	21
	137-146	1.5		26
	147-156	0.4		6
	157-166	0.9		11
	167-186	1.1		11
	187+ over	0.8	3	6
220-244	Total	22.3	23	334
	<117	0.6		20
	117-126	2.9	8	69
	127-136	4.7	2	83
	137-146	5.5	6	81
	147-156	2.4	3	29
	157-166	1.5	1	15
	167-186	3.1	2	27
	187+ over	1.6	1	10
245-259	Total	11.6	8	136
	<117	0.5		14
	117-126	1.3		24
	127-136	2.3		33
	137-146	2.0	3	23
	147-156	1.9	2	19
	157-166	1.3		11
	167-186	0.7	2	5
	187+ over	1.5	1	7
260-284	Total	16.0	23	156
	<117	1.0	1	22
	117-126	1.4	5	22
	127-136	2.1	2	26
	137-146	3.5	2	34
	147-156	1.9	4	16
	157-166	1.7	2	13
	167-186	2.7	6	15
	187+ over	1.5	1	7
285+ over	Total	18.9	18	130
	<117	0.7		11
	117-126	1.7	1	19
	127-136	3.1	4	28
	137-146	3.1	4	23
	147-156	2.8	1	16
	157-166	2.5	4	12
	167-186	3.2	3	14
	187+ over	1.9	1	7

*Expected number of cases = $\frac{\text{(population at risk)}}{(1 + e^{[\text{constant} + \text{coefficients} \times \text{variables}]})}$

Note: Cholesterol determinations were done by the Kendall-Abel method at Framingham, Massachusetts

he derived his equation. We doubt the validity of the application of Cornfield's equation to Table 16 in the Inter-Society Report in view of the latter's simplifications and the omission of the risk of experimental alteration in serum cholesterol levels which Cornfield mentions. According to the Commission's attitude, this risk would be zero. The Commission implies that the reduction mentioned in the footnote to Table 16 would only be valid for the very high levels of serum cholesterol found in hypercholesterolemia, but Cornfield claims his formula is valid for the whole range of cholesterol levels.

A total of 1329 male persons between the ages of 40 to 59 were examined for freedom of coronary heart disease in the Framginham Study. Neither then (1962) nor at the present time can even the most astute diagnostician say with certainty that an individual is free of coronary heart disease. So one of the basic assumptions of the Framingham Study is open to serious doubt.

Of the 1329 allegedly coronary heart disease-free persons only 92 developed various incidents of coronary heart disease, which must have included angina pectoris. Seventy-four were distributed over a range of cholesterol from 200 to 284 mgs per cent, with groupings as high as 23 to a low of 2 persons. The groupings were arbitrarily chosen as shown in Table II reprinted from Cornfield's paper (see at left). A questionable transformation takes place by semantic legerdemain on the part of the Commission. The *risk* of coronary heart disease in 92 persons out of a group of 1329 reported by Cornfield is equated by the Commission to the *incidence* of coronary heart disease in many millions of the U.S., if not the world's, population — a substitution which is unacceptable. Again, we doubt the accuracy of the data presented to the computer.

It is a known fact that cholesterol in the non-fasting individual, as tested in Framingham, is not greatly affected by dietary intake of fats and cholesterol in the short run. From values of our own study, described below, as well as from the world literature we learn that the same individual has variable values of serum cholesterol on different days, different seasons and other circumstances.[3]

Cholesterol was determined in five males and five females of an age group from 18 to 30 on two different occasions. On one occasion a low caloric breakfast was served consisting of two ounces of Ovaltine** dissolved in twelve ounces of milk.

**Ovaltine contains protein (10%), easily emulsified fat (1%) and carbohydrates (7%). Each teaspoonful contains 22 calories.

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Source: https://www.industrydocuments.ucsf.edu/docs/rrlk0000

TABLE III

SCATTERED VALUES OF SERUM CHOLESTEROL IN A GROUP OF INDIVIDUALS AT VARIOUS TIMES

Key:

○ = Low caloric diet, fasting
□ = High caloric diet, fasting
◉ = Low caloric diet, post-prandial
◘ = High caloric diet, post-prandial

Group A–G is male **Group H–N is female**

Patient→ Serum Level ↓	A	B	C	D	E	F	G	H	I	J	K	L	M	N
150–159										◘				
160–169		◘												
170–179				◉	□					□	□ ◘			
180–189			□		○ □ ◉	□				◉				□
190–199		○ ◉	◘	○				□ ◘		○	○			◘
200–209			◉	◘		◘					◉		□ ◘	
210–219		□	○	□			◘	○ ◉						
220–244	◘						□		C □ ◉			○ □ ◘		
245–259	◉								□			◉		
260–284	○ □													

Note: Accuracy of determinations, by the Libermann-Burchardt method, was ±3.5%.

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Source: https://www.industrydocuments.ucsf.edu/docs/mk0000

On a subsequent day a high caloric breakfast consisting of bacon, eggs, sausages, bread, butter, and orange juice was consumed. Post-prandial blood specimens were examined 15 minutes after the individual finished eating the low caloric meal. Ninety minutes after the high caloric meal post-prandial blood specimens were examined. Four individuals (2 males and 2 females) aged between 30 and 62 consumed the high caloric meal with an addition of 2 ounces of Ovaltine® in 12 ounces of milk. Fasting and 90 minutes post prandial specimens were examined. There was a total of 48 different cholesterol determinations.

It was found that only eight times did the fasting and post prandial specimens pair (see Table III, page 00). The other pairs of fasting and post-prandial values varied significantly in the same individual and projecting this finding to the Framingham Study, 66% of the post-prandial values used in this population group might be subject to grouping changes—a factor that would throw the application of Cornfield's equation to the Framingham Study into serious doubt.

The Framingham blood specimens were taken when convenient to the volunteers regardless of diet, time of the day, or other anamnestic influences. The accuracy of our determinations was ±3.5% as determined by duplicates. If hypercholesterolemia is defined as serum values over 260 mgs per cent, only one individual had such a fasting serum value, and that went down 20-40 mgs per cent post-prandially, jumping two of Cornfield's sample groups. It is also quite presumptuous to project or generalize findings found in a homogeneous northeastern community whose racial and ethnic background is not given and which could have completely different eating habits to embrace the considerable diversity of the United States population. It has been reported by others in epidemiological studies that the death rate from coronary heart disease is different in various states of the Union.[4]

Due to the narrow range chosen by Cornfield in his groupings, an individual's cholesterol level could shift from one of Cornfield's cholesterol groups into another, from day to day, and week to week. This would also apply to blood pressure measurements. These shifts would then raise havoc with Cornfield's formula. Again we find Cornfield's formula palpably wanting biologically though statistically valid, assuming the constancy of starting values.

Cornfield also stresses the fact that the percentage reduction of cholesterol pertains to risk of coronary heart disease in all values of the table high or low. But it is different if one considers the presentation of risk in actual milligram per cent reduction. There we have a large absolute difference in risk when added to a large, rather than to a small, initial level of serum cholesterol.

With complete disregard of the above considerations, the Commission devised its own interpretation of Cornfield's data. Instead of *risk*, we are now told that the coronary heart disease *incidence* is reduced with a relative reduction in serum cholesterol. According to Webster's Dictionary, 2nd edition, risk and incidence have two completely unrelated meanings—

Incidence: act, fact, manner of falling upon or affecting, range of occurrence or influence
Risk: degree of probability of loss or chance of loss

We are now told that a 10% reduction of cholesterol in the population of the United States will yield a decrease of 24.4% in the *incidence* of coronary heart disease. From Table 16 in the Commission's report we can learn that a 50% decrease in serum cholesterol will yield a decrease of 84.2% of the *incidence* of coronary heart disease. Any biologically oriented researcher knows that this is a physiologic impossibility and is absurd in its implication because a 50% reduction of serum cholesterol levels may entail untold dangers.

Cornfield must have sensed these shortcomings because in a later (1969) publication[5] he stated, "We must admit at the outset that we have no secure basis for estimating the reduction in incidence of or mortality from coronary heart disease that could be achieved by application of current knowledge." He also states in the same article, "It seems clear that despite a very considerable scientific effort and some tantalizingly suggestive results, we have no clear-cut generally accepted answer to the question whether cholesterol lowering measures can affect coronary heart disease." We concur in Cornfield's doubts. We feel that his equation is not valid biologically and should not be used to substantiate the implied effect of proposed dietary changes suggested by the Commission.

Obsessed with the idea of correlating values from blood chemistry with actual disease, the Commission was undisturbed by reality and objectivity. Since the Commission's mind was made up in advance, the membership of the Commission did not want to be bothered with the confusing facts. For example, in a study of cigarette smoking, the find-

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Source: https://www.industrydocuments.ucsf.edu/docs/rrlk0000

ings of Keys and others[2] that there was no connection between cigarette smoking and coronary heart disease in certain European countries was not mentioned, whereas the findings concerning the relationship between cholesterol levels and coronary heart disease in the same study are given prominence. Keys also states in the same study, again not mentioned in the Commission's Report, that the incidence of coronary heart disease is lower among individuals who smoke less than 20 cigarettes per day than among *nonsmokers* or heavy smokers. An unbiased report would not have solicited from such omissions.

In a very recent study by Keys[3] we find that in contrast to a value of 2.66 found in the Framingham Study as the exponent for coronary heart disease incidence, a value of 2.21 has now been established. There is also a presentation that angina pectoris was less closely related to serum cholesterol level than it was to myocardial infarction. This result is also duplicated by a study of Western Electric Co employees and Los Angeles civil servants.[4] However, as mentioned before by Gofman[5] in his paper[6] all phases of coronary heart disease are included in the Framingham Study. This again shows the unreliability of his original data.

Furthermore, the statements of Pearce and Dayton,[7] who warn that their findings are not to be construed as recommending reductions in the American diet, are alarmingly absent in the Commission's Report. Due to their caveats regarding potential dangers from unregulated fats in the American diet, a misunderstanding is understandable. The American people are led to believe that unsaturated fatty acids do not undergo chemical changes such as hydrogenation during cooking, though such changes do take place. Little is known of the extent of such chemical changes in the Inter-Society Commission Report.

If publications of the individual members concerning the Commission are examined, one finds that in July 1970 [8] Dayton wrote an editorial "in the American Journal of Medicine" about the prevention of coronary heart disease. The conservative physician must agree that, although the data are suspect, the consensus opinion and the environmental principle that he should do no harm. In December of the same year one finds Dayton, a member of the Commission giving his opinion to other physicians on modifications of dietary changes.

A more cautious view of such dietary changes is reflected in the remarks of Dr. Donald S. Fredrickson, who chaired the Inter-Society Commission Report in his St. Cross Lecture[9] at the National Heart Hospital at the Royal College of Physicians of London, published in the British Medical Journal:[10]

> "Here are some things about the report to be pointed out in the light of what is actually known. The unproved component of cholesterol and fats seems to be the basis of the stand. What evidence do we have that an egg a day spells peanuts for all Americans? . . .
>
> ". . . One looks vainly in the Commission Report for something new and strong enough to change the present fundamental non-position concerning dietary fat restriction. . . ."

The Commission disregards the potential economic dislocations which would result from their recommendations, should they become realized. It also completely disregards the warnings and excellent deliberations in the Report of the Ad Hoc Heart Review Panel of the National Heart Institute dated June 1960 and published as American Heart Association Monograph No. 28, 1969, which antedates the Inter-Society Commission Report. The members of that panel have at least the same scientific standing and authority, but act more responsibly than the members of the Inter-Society Commission.

By critical analysis of the Report of the Inter-Society Commission for Heart Disease Resources concerning the prevention of atherosclerosis we are led to endorse the opinions of Ludwig and Co-Workers[11] "Errors of presentation include inappropriate generalizations and the incautious use of questionable data." We feel that the Commission presented its findings in a misleading manner.

We quote again from Ludwig and Co[11] "More serious consequences follow when erroneous conclusions are drawn from invalid data or from faulty or incomplete analyses. Health programs may be augmented or discontinued, beneficial practices modified, and worthless solutions to problems advanced, all on the basis of misinformation."

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Stamler (*49*) has analyzed the data on 13 deaths occurring during the first years of the Chicago Coronary Prevention Evaluation Program, which originally consisted of 519 coronary-prone male volunteers aged 40 to 59 who were free from clinical CHD. Eleven of the 13 decedents had three or more coronary risk factors at entry into the program, and at least 8 were cigarette smokers at the time of death. Forty-three men, who were cigarette smokers at entry into the Coronary Prevention Evaluation Program, gave up smoking and have remained active in the program. There have been no deaths from cardiovascular causes in this group. Stamler (*49*) commented: "Even though the number of decedents was small, these data strongly suggest that continued cigarette smoking is associated with very high risk of premature death for very coronary-prone men, and that other preventive measures are by themselves of limited value for them as long as they fail to give up cigarette smoking."

As described in the 1971 report, "The Health Consequences of Smoking" (*56*), some studies have indicated that smokers show increased levels of serum lipids while others have not. Such contradictory results are also present in recent studies from Germany, Poland, and Sweden (*21, 39, 53*).

After a patient suffers a myocardial infarction, he frequently gives up smoking (*17, 26*). Only fragmentary data are available on what effect the cessation of cigarette smoking might have on the likelihood of a recurrent myocardial infarction (*9, 34, 43*). Ninety-two survivors of a first myocardial infarction were studied over a 3-year period by Parás Chavero, et al. (*43*). During this time, 37 patients continued smoking, and 12 of them (32 percent) experienced a second myocardial infarction. The 51 patients who did not smoke during this 3-year period included 39 ex-smokers and 12 patients who had never smoked. Eight of the nonsmokers (16 percent) experienced a second myocardial infarction. The smoking habits of four of the patients were not known. Although the continuing smokers experienced a greater rate of recurrent myocardial infarction than the nonsmokers, the difference was not statistically significant ($P = .07$).

The role of genetic factors in the development of CHD and the difficulties associated with the use of twin studies were discussed in the 1971 report, "The Health Consequences of Smoking" (*56*). Mailed questionnaires were used to establish the diagnosis of angina pectoris in a study by Lundman, et al. of twin pairs discordant with respect to smoking habits and in a study by Liljefors of twins with CHD. Lundman, et al. (*36*) recently investigated 69 male twins with the diagnosis of angina pectoris established by questionnaire. Only 22 percent of these diagnoses could be verified by clinical examination.

In a study of CHD, Liljefors (*35*) studied 91 pairs of twins from the Swedish Twin Registry of 1967. The twins ranged in age from 42 to 67 years, and 51 pairs were monozygotic. Smoking habits were not significantly different in pairs discordant for the probable presence of CHD. However, Liljefors noted that "... in many pairs the smoking habits were similar and that the material included few pairs discordant with respect to smoking, so that it does not provide a suitable basis for conclusions as to the causal importance of smoking for CHD." As observed in the 1971 report, "The Health Consequences of Smoking" (*56*), it would be surprising if genetic factors did not play a role in heart disease; however, it is open to question whether findings from twin studies can be used to distinguish between "... the hypothesis that genetic factors govern the level of host susceptibility or resistance to the effects of an exogenous influence such as cigarette smoking and the hypothesis that genetic factors 'cause' both heart disease and smoking."

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Source: https://www.industrydocuments.ucsf.edu/docs/rrk0000

Prognosis of Myocardial Infarction. The details of (34) Leren's investigation are not recounted. The results do not show that smoking is related to mortality rate. The details are as follows:

Smoking Habits

Smoking habits were about the same in the two groups at entry and showed practically no change during the first 5 years of the trial. Because of the frequent combination of self-rolled cigarettes and a pipe, it was impossible to consider cigarette smokers alone. Table 10 presents the overall CHD mortality rate in relation to smoking habits. The death rate in the smokers tends to be higher than in the nonsmokers. However, the difference is small and not statistically significant. The incidence of sudden death was the same (20.3 and 20.5%) in smokers and nonsmokers. Smoking was not related to the serum cholesterol level.

Combined Risk Factors

Figure 5 evaluates the importance of an elevated serum cholesterol level as a risk factor in the presence of hypertension in smokers. The CHD mortality rate was three

Table 10

Eleven-Year Incidence of CHD Deaths in Relation to Smoking Habits: Both Groups Combined

	Nonsmokers	Smokers
At risk	146	266
Age (yr)	57.1	55.8
Cholesterol (mg 100 ml)	271	268
CHD deaths	54	119
%	37.0	44.7

times higher in the hypertensive smokers wi a cholesterol level above 250 compared wi normotensive nonsmokers with a cholester level below 250. This difference is high significant ($P = 0.007$).

Epidemiologic studies have demonstrated several factors associated with the risk of developing first manifestations of coronary heart disease. Blood lipids, blood pressure, and cigarette smoking are such risk variables. The present study demonstrates that these factors, all amenable to control, are of prognostic significance even after a myocardial infarction. When combining data from both groups, a three-fold greater CHD mortality rate is demonstrable among the hypercholesterolemic, hypertensive smokers than among those in whom these factors were low or absent. In spite of the small numbers this observation lends some support to the view that the multifactorial approach is the best way to the solution of the coronary heart disease problem.

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AUTOPSY STUDIES

In previously reported autopsy studies, Auerbach, et al. found that aortic and coronary atherosclerosis in man were more common and severe among smokers than among nonsmokers (*5*). They have now extended their investigations to the myocardial arterioles of men and beagle dogs (*6*). In a study of 1,184 men, they found that the thickness of myocardial arteriole walls was greater, on the average, in smokers than nonsmokers (table 3). The thickness increased with the number of cigarettes smoked per day and with age. The thickness was less, on the average, among cigar and pipe smokers than among cigarette smokers, but it was greater than in men who had never smoked regularly.

TABLE 3.—*Human autopsy study. Comparison of the thickness of myocardial arteriole walls in smokers and nonsmokers.*[1]

Age (years)	Smoking	Number of Men					Percent of Men		
		Total	‡Grade 0	‡Grade 1	‡Grade 2, 3	Total	‡Grade 0	‡Grade 1	‡Grade 2,3
<45	None	22	2	19	1	100.0	9.1	85.4	4.5
	Cigar, pipe	4	—	1	3	100.0	—	†25.0	†75.0
	Cig. 1–19	50	1	31	18	100.0	2.0	62.0	36.0
	Cig. 20–39	85	4	35	46	100.0	4.7	41.2	54.1
	Cig. ≥40	29	—	10	19	100.0	—	34.5	65.5
45–59	None	15	1	12	2	100.0	6.7	80.0	13.3
	Cigar, pipe	13	—	8	5	100.0	—	61.5	38.5
	Cig. 1–19	33	—	17	16	100.0	—	51.5	48.5
	Cig. 20–39	99	—	35	64	100.0	—	35.4	64.6
	Cig. ≥40	50	—	11	39	100.0	—	22.0	78.0
60–69	None	56	4	36	16	100.0	7.1	64.3	28.6
	Cigar, pipe	35	—	22	13	100.0	—	62.9	37.1
	Cig. 1–19	92	—	44	48	100.0	—	47.8	52.2
	Cig. 20–39	193	—	58	135	100.0	—	30.1	69.9
	Cig. ≥40	87	—	21	66	100.0	—	24.1	75.9
≥70	None	32	2	18	12	100.0	6.3	56.2	37.5
	Cigar, pipe	40	—	19	21	100.0	—	47.5	52.5
	Cig. 1–19	30	—	12	18	100.0	—	40.0	60.0
	Cig. 20–39	46	—	12	34	100.0	—	26.1	73.9
	Cig. ≥40	9	—	3	6	100.0	—	†33.3	†66.7

[1] In the right ventricular wall of 1,723 men by age and smoking habits.
† Percentages based on less than ten cases.
‡ Four Point Scale for the Thickness of Myocardial Arteriole Walls:
0—normal thickness. 1—slight thickness; 2—moderate thickness; 3—great thickness.

SOURCE: Auerbach, O., et al. (*6*).

(*5*) AUERBACH, O., HAMMOND, E. C., GARFINKEL, L. Smoking in relation to atherosclerosis of the coronary arteries. New England Journal of Medicine 273(15): 775–779, October 7, 1965.
(*6*) AUERBACH, O., HAMMOND, E. C., GARFINKEL, L., KIRMAN, D. Thickness of walls of myocardial arterioles in relation to smoking and age. Archives of Environmental Health 22(1): 20–27, January 1971.

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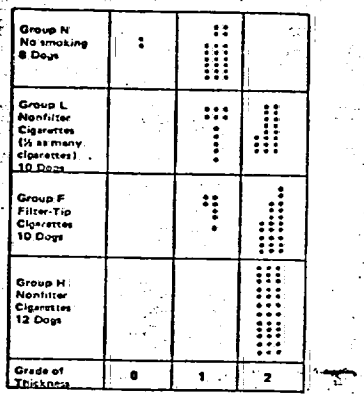
In one experiment, beagle dogs inhaled cigarette smoke daily through tracheostomae. Twenty-eight dogs that died between days 67 and 875 formed one group; 32 dogs that were killed after 875 days formed another group. Eight control dogs were not exposed. Beagle myocardial arteriole walls were found to be thicker in smoking than nonsmoking dogs, in dogs smoking many cigarettes than in dogs smoking fewer cigarettes, and in dogs smoking nonfilter cigarettes than in dogs smoking filter-tip cigarettes (figure 1). Also, the thickness of arteriole walls increased with the duration of smoking.



Each dot represents one section. The three dots on a line represent the three sections from a particular dog.

FIGURE 1.—Canine autopsy study. Comparison of the thickness of myocardial arteriole walls in 32 smoking dogs killed after 875 days and 8 nonsmoking dogs.

SOURCE: Auerbach, O., et al. (6).

EXPERIMENTAL STUDIES

NICOTINE AND CIGARETTE SMOKE

Schievelbein, et al. (47) investigated the effect of oral nicotine administration over a 20-month period on lipid metabolism in 35 rabbits. Even though lipoprotein lipase levels and calcium content of the aorta were significantly greater in the group given nicotine than in the control group, the histological changes of arteriosclerosis were found with equal frequency in both groups. The authors concluded that the epidemiological correlations between CHD and cigarette smoking could not be explained by the pharmacologic effect of nicotine alone.

A study of the interaction of chronic nicotine administration and acute hypoxia in 280 rats was performed by Wenzel and Richards (60). Pretreatment of the rats with nicotine increased the mortality during hypoxia, but the difference was not statistically significant. Pretreatment with the nicotine also was associated with marked variability of regression of hypoxic heart lesions. The interaction of nicotine pretreatment and the hypoxic insult produced variable effects on myocardial enzymes.

Aronow (1) recently studied the effect of cigarette smoking on the A wave of the apexcardiogram in 20 men with CHD. The A wave reflects the left ventricular filling wave associated with the impact of blood upon the ventricular wall during left atrial contraction. He found that the mean maximum increase in A wave ratio after smoking was 34 percent for high-nicotine cigarettes, 13 percent for the low-nicotine cigarettes, and 6 percent for the non-nicotine cigarettes. He ascribed these changes to increased myocardial ischemia produced by cigarette smoking, which was reflected by a larger A wave ratio in the apexcardiogram. While nicotine appears to have produced most of these changes, the observation that a 6 percent increase occurred in the absence of nicotine suggests the possibility that carbon monoxide plays a role in this effect.

(47) SCHIEVELBEIN, H., LONDONG, V., LONDONG, W., GRUMBACH, H., REMPLIK, V. Nicotine and arteriosclerosis. An experimental contribution to the influence of nicotine on fat metabolism. Zeitschrift für Klinische Chemie und Klinische Biochemie 8(3): 190–196, May 1970.

(60) WENZEL, D. G., RICHARDS, M. H. Effects of chronic nicotine, acute hypoxia, and their interactions on myocardial enzymes. Toxicology and Applied Pharmacology 16(3): 656–667, May 1970.

(1) ARONOW, W. S. The effect of smoking cigarettes on the apexcardiogram in coronary heart disease. Chest 59(4): 365–368, April 1971.

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Histological Evidence of Atherosclerosis. The technique of measuring thickness of the wall only unrelated to the size of the lumen has been severely criticized. The accepted technique is wall to lumen ratio. Anyway, in the Discussion (6) Auerbach et al. recognize the problem relating to the cause of the thickness. If some measurements were taken prior to sacrificing the animals, the possibilities enumerated could have been explored. Furthermore, in the absence of functional measurements, it is impossible to detect ischemia.

It would be important to determine what ingredients of cigarette smoke are responsible for the greater thickness of walls of arterioles in smoking dogs than in dogs not exposed to cigarette smoke. As described above, the thickness was less on the average, in dogs that smoked filter-tip cigarettes than in dogs that smoked nonfilter cigarettes. The cellulose acetate filter used in this experiment resulted in a reduction of both tar and nicotine. This suggests that tar or nicotine or a combination of the two is responsible for the effects of smoking upon the thickness of walls of arterioles in the myocardium. However, in light of the findings of Harkavy[4] and the findings of Wanstrup, Kjeldsen, and Astrup[5] in experiments carried out on rabbits, we cannot rule out the possibility that allergy to tobacco proteins or that CO in cigarette smoke may have contributed to the observed effect of cigarette smoking upon the thickness of walls of arterioles in the myocardium of the beagle dogs.

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Carbon Monoxide

Because cigarette smoke contains from 2.7 to 6 percent carbon monoxide (CO), significantly higher carboxyhemoglobin (COHb) levels are found in smokers than nonsmokers (4, 20, 25, 62). COHb levels in nonsmokers are usually less than 1 percent, while those in smokers average around 4 percent and may exceed 15 percent (4, 20, 56). Heavy smokers and those who inhale show the highest carboxyhemoglobin levels (20).

Haebisch (24) found that a smoker with a daily consumption of 35 to 40 cigarettes easily attains and maintains for hours an alveolar CO concentration of 50 p.p.m., which reaches or exceeds legally-established ambient air quality standards (14, 18, 23, 24).

Cohen, et al. (13) and Aronow, et al. (2) have shown that there is no significant difference in mean expired air carbon monoxide levels after patients have smoked tobacco or lettuce leaf cigarettes. Although pipe and cigar smokers in the United States are reported to have lower exposure to CO than cigarette smokers (20), CO intoxication has been reported in cigar smokers (25).

CO exerts its adverse effects on the cardiovascular system of smokers through one or more of the following mechanisms: (a) reduction of the amount of hemoglobin available for oxygen transport; (b) shift of the oxygen-hemoglobin dissociation curve to the left with consequent interference in oxygen release at the tissue level; and (c) induction of arterial hypoxemia. CO may interfere with the homeostatic mechanism by which 2,3-DPG controls the affinity of hemoglobin for oxygen (56). CO has also been implicated in experimental atherogenesis in animals (56).

Ayres, et al. (7) recently studied 41 patients during diagnostic cardiac catheterization, at which time they inhaled either 5 percent or .1 percent CO. Arterial and mixed venous oxygen tensions were decreased by administration of either concentration. In patients with CHD, coronary artery O_2 extraction decreased 7.9 percent after inhalation of .1 percent CO and 30.5 percent after inhalation of 5 percent CO. Some of the patients with CHD experienced changes in lactate and pyruvate metabolism indicative of inadequate myocardial oxygenation. The higher level of CO inhalation in this experiment is comparable to that experienced intermittently by cigarette smokers.

Brewer and his colleagues (11) investigated cigarette smoking as a cause of hypoxemia in residents of Leadville, Colorado, at an altitude of 3,100 meters. The arterial pO_2 of 8 smokers was significantly lower ($P < .05$) than that of 12 nonsmokers, but this was reversible upon cessation of smoking. They concluded that the adverse effect of cigarette smoking on O_2 transport may be especially pronounced at high altitude and may restrict an individual's ability to adapt to reduced O_2 tensions (11, 12).

Kjeldsen (31, 32) examined 933 industrial workers, about one-half of whom were tobacco workers. Fifty-nine cases of arteriosclerosis were documented by such clinical symptoms as angina pectoris and intermittent claudication or by a previous history of myocardial infarction. While 20.9 percent of the 934 "control" individuals were nonsmokers, only 2 (3.4 percent) of the 59 patients with arteriosclerosis were nonsmokers. A significantly higher percentage of diseased workers were heavy smokers and inhaled the smoke.

Cholesterol Content of Tobacco and Tobacco Smoke

Cholesterol glucoside has not previously been reported in tobacco, or in any other plant (10). Bolt and Clarke (10) investigated the sterolin and sterol fraction of flue-cured tobacco and found that cholesterol is one of the major components of the sterol fraction.

More recently, Grunwald, et al. (22) have confirmed that cholesterol accounts for 10 percent of the total sterol in cigarette tobacco. They also found that 8.6 percent of the total sterol content of cigarette smoke condensate was cholesterol. Thirteen percent of the cholesterol present in cigarette tobacco was transferred to the condensate.

The biological significance of these findings remains to be determined.

(13) Cohen, S. I., Perkins, N. M., Utey, H. K., Goldsmith, J. R. Carbon monoxide uptake in cigarette smoking. Archives of Environmental Health 22(1): 55–60, January 1971.

(20) Goldsmith, J. R. Contribution of motor vehicle exhaust, industry, and cigarette smoking to community carbon monoxide exposures. Annals of the New York Academy of Sciences 174(1): 122–134, October 5, 1970.

(24) Haebisch, H. Die Zigarette als Kohlenmonoxydquelle. (The cigarette as a source of carbon monoxide.) Archiv fur Toxikologie 26(3): 251–267. August 26, 1970.

(62) Wynder, E. L., Hoffmann, D. Tobacco and Tobacco Smoke. Studies in Experimental Carcinogenesis. New York, Academic Press, 1967. 730 pp.

(4) Astrup, P., Kjeldsen, K., Wanstrup, J. Effects of carbon monoxide exposure on the arterial walls. Annals of the New York Academy of Sciences 174(1): 294–300, October 5, 1970.

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(18) Environmental Protection Agency. National primary and secondary ambient air quality standards. Federal Register 36(84): 8186–8201, April 30, 1971.

(23) Gelt, A., Astrup, P., Chalken, P. J. R., Gerhardsson, G. Threshold limit values for carbon monoxide. Archives of Environmental Health 21(4): 542–544, October 1970.

(2) Aronow, W. S., Denduinger, J., Rokaw, S. N. Heart rate and carbon monoxide level after smoking high-, low-, and non-nicotine cigarettes. A study in male patients with angina pectoris. Annals of Internal Medicine 74(5): 697–702, May 1971.

(25) Hamill, W., O'Neill, R. P. Carbon monoxide intoxication in cigar smokers. Irish Journal of Medical Science 2(6): 273–277, June 1969.

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(32) Kjeldsen, K. Rökning och koronarsjukdom (12): CO-exposition og aterosclerosefrekvens. (Smoking and coronary diseases (12): Exposure to carbon monoxide and frequency of atherosclerosis.) Lakartidningen 67(3): 262–265, January 14, 1970.

(10) Bolt, A. J. N., Clarke, R. F. Cholesterol glucoside in tobacco. Phytochemistry 9(4): 819–822, April 1970.

(22) Grunwald, C., Davis, D. L., Rush, L. P. Cholesterol in cigarette smoke condensate. Journal of Agricultural and Food Chemistry 19(1): 128–133, January–February 1971.

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Atherosclerosis and Carbon Monoxide. The results of (31, 32) Kjeldsen should be compared with the negative results of Petrovská and Draková (1967 and 1971). They examined individuals who have been exposed to an environment of up to 1,000 ppm carbon monoxide and blood levels of 2 to 26% for 10.5 years. These individuals did not develop any early lesions of atherosclerosis.

PREROVSKÁ I and DRDKOVÁ S: Vliv chronickeho pusobeni kyslicniku uhelnateho na biochemicke zmeny v seru vzbledem k aterosklerose. (The effect of chronic exposure to carbon monoxide on biochemical changes in the blood with respect to atherosclerosis). Prac Lek 19: 1-4, 1967a.

PREROVSKÁ I and DRDKOVÁ S: Vliv chronickeho pusobeni prumyslovych skodlivin na exponovane pracovniky vzhledem k rozvoji aterosklerozy. (Influence of the chronic action of industrial anoxious agents on exposed workers in relation to the development of atherosclerosis). Cas Lek Cesk 106: 754-759, 1967b.

PREROVSKÁ I and DRDKOVÁ S: Der Einfluß der chronischen Einwirkung von Kohlenoxyd auf den klinischen Zustand und biochemische Veranderungen im Serum exponierter Personen in Hinsicht auf die vorzeitige Entwicklung der Atherosklerose. (Influence of chronic action of carbon monoxide on the clinical status of biochemical changes in the serum of exposed persons on development of atherosclerosis with influence to the premature). Int Arch Arbeitsmed 28: 175-188, 1971.

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COR PULMONALE (PULMONARY HEART DISEASE)

The relationship between cigarette smoking and chronic obstructive bronchopulmonary disease (COPD) with cor pulmonale was discussed in the 1968 Supplement to "The Health Consequences of Smoking" (*55*).

Although the extent of morbidity and mortality due to cor pulmonale and right heart failure is difficult to determine, COPD is often complicated by these conditions (*27*).

The Pulmonary Heart Disease Study Group of the Inter-Society Commission for Heart Disease Resources recently summarized the evidence linking cigarette smoking with COPD and concluded: "Cigarette smoking is the major cause of pulmonary heart disease in that it is the most important cause of the chronic non-neoplastic bronchopulmonary diseases in the United States" (*28*).

CEREBROVASCULAR DISEASE

The 1971 report, "The Health Consequences of Smoking" (*56*), summarized the data linking smoking to cerebrovascular disease as follows:

1. Data from numerous prospective studies indicate that cigarette smoking is associated with increased mortality from cerebrovascular disease.
2. Experimental evidence concerning the relationship of smoking and cerebrovascular disease is at present insufficient to allow for conclusions concerning pathogenesis. However, some of the pathophysiological considerations discussed concerning CHD may also pertain to the relationship of smoking and CVD, particularly cerebral infarction.

In the interim, additional reports have been published.

Dyken (*15*) performed a retrospective study on 285 patients with cerebrovascular disease in Elkhart, Indiana. Even though low cigarette consumption was noted in all groups, males who had cerebral infarctions smoked significantly more than controls.

Paffenbarger, et al. (*42*) found that smokers of more than 20 cigarettes a day faced a slightly increased but not significantly greater risk of dying from a stroke than those smoking lesser amounts.

After 16 years follow-up, male cigarette smokers in the Framingham study had more than three times the nonsmokers' risk of developing a cerebral infarction (*29*). However, Kannel commented: "It is not clear that smoking actually affects the rate of cerebral atherogenesis, and some other mechanism may be involved."

(*15*) DYKEN, M. L. Precipitating factors, prognosis, and demography of cerebrovascular disease in an Indiana community: A review of all patients hospitalized from 1963 to 1965 with neurological examination of survivors. Stroke 1(4): 261–269, July-August 1970.

(*29*) KANNEL, W. B. Current status of the epidemiology of brain infarction associated with occlusive arterial disease. Stroke 2(4): 295–318, July–August 1971.

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PERIPHERAL VASCULAR DISEASE

The 1971 report, "The Health Consequences of Smoking" (*56*), summarized the data relating smoking to peripheral vascular disease as follows:

1. Data from a number of retrospective studies have indicated that cigarette smoking is a likely risk factor in the development of peripheral vascular disease. Cigarette smoking also appears to be a factor in the aggravation of peripheral vascular disease.

2. Cigarette smoking has been observed to alter peripheral blood flow and peripheral vascular resistance.

Newly published studies add to our understanding of the effect of nicotine or tobacco smoke on the peripheral circulation and of the significance of smoking in peripheral vessel atherogenesis.

Martz, et al. (*37*) observed that some of the apparently conflicting data on the effects of nicotine upon the peripheral vasculature may result from interpretations based upon indirect measurements of microcirculatory variables. Hence, they studied vascular changes in a bat wing under direct microscopic observation. They noted a marked increase in the diameter of innervated, minute arteries with intraperitoneal nicotine administration, but this effect was abolished with sympathetic denervation.

Asano and Branemark (*3*) installed a direct, microscopic observation chamber in the connective tissue of two human volunteers. One volunteer was a "healthy" 20-year-old male nonsmoker. The other volunteer was a diabetic who had been a smoker for five years and who "...had no apparent diabetic vasculopathy." The effects of tobacco smoking on the microcirculation of these volunteers included: "...vasoconstriction, decrease in blood flow rate and frequency of plasma spacing, blocking of blood flow in varying numbers of nutritive capillaries, shunting of blood from arterioles to venules...." These microcirculatory changes were said to result in a decrease of nutritive blood flow in tissue.

As mentioned in the discussion of CHD, Kjeldsen (*31, 32*) studied several smoking patients with occlusive peripheral vascular disease whose COHb levels were significantly higher than those of control smokers. The levels of COHb in many of these patients were comparable to those associated with experimental atherosclerosis in animals. Astrup, et al. (*4*) have suggested that prospective studies should be performed to investigate the relationship between COHb levels and the incidence of arterial disease.

In the Prague study (*19*) intermittent claudication was significantly ($P < .01$) more common among cigarette smokers than nonsmokers. Twenty percent of the men in the age group of 60 to 64 who were heavy smokers (more than 25 cigarettes a day) had intermittent claudication.

Råf (*44*) reported that all but 4 of the 98 patients admitted for peripheral vascular surgery at the Karoline Hospital, Sweden, were smokers.

Mathiesen, et al. (*38*) in Denmark followed the spontaneous course of arterial insufficiency in 211 patients. Cessation of smoking increased the number of patients displaying spontaneous improvement.

ORAL CONTRACEPTIVES, THROMBOPHLEBITIS, AND SMOKING

In two studies from Great Britain and one from the United States, it was reported that the use of oral contraceptives was associated with a significantly increased risk of developing venous thromboembolism (*46, 58, 59*). The British investigators also noted in their initial report that the affected patients were, on the average, heavier smokers than controls (*58*). However, after an additional year of study, a similar effect was not noted and they concluded (*59*): "...the earlier difference between the smoking habits of the two groups can thus reasonably be attributed to chance ($P = 0.08$)." The American investigator (*45*) found "...no evidence that smoking, acting either independently or in conjunction with oral contraceptives, is a factor in idiopathic thromboembolism."

Cigarette smoking has not been clearly demonstrated to be a factor that contributes to the risk of idiopathic thromboembolism associated with the use of oral contraceptives. Nevertheless, the possibility that it may act to increase that risk has not yet been completely ruled out.

(37) Martz, R. C., Youkilis, E. J., Harris, P. D., Forney, R. B., Nicoll, P. A. Effects of nicotine on the subcutaneous microcirculation of the bat. Proceedings of the Society for Experimental Biology and Medicine 133(1): 153–159, January 1970.

(3) Asano, M., Branemark, P.-I. Cardiovascular and microvascular responses to smoking in man. Advances in Microcirculation 3: 125–153, 1970.

(44) Råf, L. E. Medicinska skadeverkningar av rökning. Rökning och perifera kärlsjukdomar. (Harmful clinical effects of smoking. Smoking and diseases of the peripheral vessels.) Social-Medicinsk Tidskrift 2 (Special No.): 67–71, February 1971.

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(58) Vessey, M. P., Doll, R. Investigation of relation between use of oral contraceptives and thromboembolic disease. British Medical Journal 2: 199–205, April 27, 1968.

(59) Vessey, M. P., Doll., R. Investigation of relation between use of oral contraceptives and thromboembolic disease. A further report. British Medical Journal 2(5558): 651–657, June 14, 1969.

(45) Sartwell, P.E. Oral contraceptives and thromboembolism: A further report. American Journal of Epidemiology 94(3): 192–201, September 1971.

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HIGHLIGHTS OF CURRENT CARDIOVASCULAR INFORMATION

In addition to the comprehensive summary from the 1971 report, "The Health Consequences of Smoking" (*56*), cited earlier in this chapter, the following statements are made to emphasize the most recent developments in the field:

1. Recent epidemiological studies from several countries confirm that cigarette smoking is one of the major risk factors contributing to the development of CHD. Avoidance of cigarette smoking is of importance in the primary prevention of CHD.
2. Studies in man and animals have shown a greater myocardial arteriole wall thickness in smokers than nonsmokers.
3. Experimental and epidemiological investigations implicate the elevation of carboxyhemoglobin levels in smokers as a contributor to the development of CHD and arteriosclerotic peripheral vascular disease.
4. Cigarette smoking is considered to be the major cause of pulmonary heart disease (cor pulmonale) in the United States in that it is the most important cause of chronic nonneoplastic bronchopulmonary diseases. Avoidance of cigarette smoking is of importance in the primary prevention of pulmonary heart disease.

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Cigarette Consumption. In 1971, Seltzer wrote a letter to the Editor (N Engl J Med 11 March, 1971) commenting on the secular rise in death rate from heart disease paralleling the secular increase in cigarette consumption. This topic has been omitted from the 1972 Document. The response of Grannis (N Engl J Med 284: 1384-1385, 1971) is also reproduced.

CIGARETTES AND HEART DISEASE

To the Editor: It has been suggested that the secular rise in death rate from heart disease parallels the secular increase in cigarette consumption. In this connection, the recently published World Health Organization's data on the death rates from arteriosclerotic and degenerative heart disease for the age group 45 to 54 and for the years 1955 to 1967 are most interesting.

Table 1 gives in rank order the percentage changes in adult per capita cigarette consumption and the appropriate

Table 1. Death Rates from Arteriosclerotic Heart Disease in Relation to Smoking.

Country	Cigarette Consumption/Adult*	Death Rate from Arteriosclerotic Heart Disease†
	Changes in % (1967/1955)	Changes in % (1967/1955)
Finland‡	− 5	+30
UK	+ 13	+29
Netherlands	+ 17	+53
US	+ 18	+ 1
France§	+ 33	+39
Switzerland	+ 38	+10
Sweden§	+ 39	+10
Italy	+ 46	+13
Canada§	+ 47	+ 8
Japan§	+ 48	−27
Australia	+ 51	+28
Austria§	+ 55	+32
W. Germany§	+200	+ 20

*Tobacco Consumption in Various Countries. Second edition. Edited by DH Bone. London, Tobacco Research Council (Research Paper 6), 1968

†Lawyer J: The modern epidemic: ischaemic heart disease. World Health, August-September, 1970, pp 3-11

‡Based on 1966 cigarette & death-rate figures from arteriosclerotic heart disease (since 1947 tobacco figures have not been available).

death rates from arteriosclerotic heart disease for the countries listed by WHO from 1955 to 1967. From this table, it appears that there is no rank-order association between cigarette consumption and death rates from arteriosclerotic heart disease. In fact, among the five countries with the smallest changes in cigarette consumption, four countries (Finland, United Kingdom, Netherlands and France) show the largest percentage increases in heart-disease mortality. Striking is Finland to plays a 5 per cent decrease in per capita cigarette consumption, and yet over the same period has experienced a 30 per cent increase in deaths from arteriosclerotic heart disease.

Of further interest is the fact that whereas Japan has had a 48 per cent increase in cigarette consumption, its death rate from arteriosclerotic heart disease over the same period has declined 27 per cent. West Germany, with a 200 per cent increase in cigarette consumption, shows only a 20 per cent increase in arteriosclerotic heart disease. For the United States the death rate from this cause is essentially unchanged, whereas our country has experienced an 18 per cent rise in per capita consumption. These data do not support the parallelism of secular changes in cigarette consumption and heart-disease mortality.

I do not draw any conclusions regarding the effect of cigarette smoking on heart-disease mortality from these figures, except to point out the danger of the use of secular changes in tobacco consumption and heart-disease mortality for this purpose. Obviously, the etiology of heart disease is far too complex for such simplistic interpretations from these kinds of statistical data.

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Harvard School of Public Health

To the Editor: C. C. Seltzer, of the Harvard School of Public Health, recently tabulated data purporting to show a poor correlation of secular changes in cigarette consumption with heart disease mortality rates (N Engl J Med 284:1357, 1971). However, the kind of statistics used (percentage changes rather than absolute changes, and combined death rates of males and females rather than death rates of males) were inappropriate for evaluating this nonexperimental, secular-trend correlation. Figure 1 puts these data in a clearer perspective.

Seltzer emphasized apparent inconsistencies such as the disproportionate changes in the Netherlands and England as compared to changes in countries such as West Germany and Canada. Figure 1 shows that the changes observed in these and many other countries were in fact in good agreement with the relation previously established in epidemiologic studies.

The purpose of Seltzer's communication may have been to point out, correctly, that factors other than cigarette smoking are important in the etiology of heart disease, particularly among nonsmokers and in countries such as Japan, France, Switzerland and especially Finland. However, the tenor of his presentation discounted the major role of cigarette smoking in causing premature mortality of males, par-

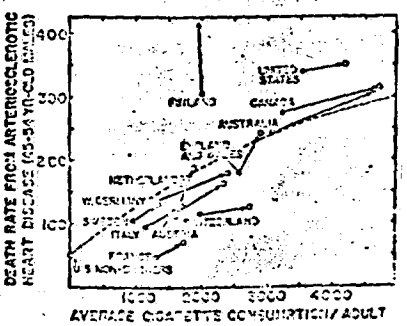

Figure 1. Average Cigarette Consumption per Adult per Year and Heart Disease Mortality (Males, 45 to 54 Years Old) Observed in Epidemiologic Studies of U.S. Men (●) and in Various Countries in 1955 (○) and 1967 (○).

The arrows show the changes that occurred in each country. The 18 per cent increase in cigarette consumption in the United States during the 5-year period shown in Figure 1 is artificial, being due to an [illegible] in the amount of tobacco per cigarette.

ticularly from heart disease, and his choice of statistics confused an otherwise clear situation.

Thus, I conclude that secular changes in heart disease mortality rates have indeed paralleled changes in cigarette consumption, confirming on a worldwide basis that cigarette smoking continues to be a major health problem that merits the concerned attention of national leadership.

The problem of cigarette smoking is serious because of the large decrease in average longevity of smokers, the large number of smokers and the long period of involvement with smoking. The problem has been well documented at all levels of scientific inquiry, and serious socioeconomic disruptions of contemporary American society caused by smoking have been noted.[1,2,3] Nevertheless, national leadership has been unable to arrive at a meaningful solution to the problem, partly because of obfuscation of issues by specious statistical interpretations.

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THE HEALTH CONSEQUENCES OF SMOKING

JANUARY 1973

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service

CHAPTER 1

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CARDIOVASCULAR DISEASES

INTRODUCTION

In the United States, coronary heart disease (CHD) is the leading cause of death and is the largest contributor to excess deaths among cigarette smokers. The following is a brief summary of the major relationships between smoking and cardiovascular diseases as outlined in previous reports of the health consequences of smoking *(62, 63, 64, 65, 66, 67)*.

Many prospective and retrospective epidemiological studies have identified cigarette smoking, elevated serum cholesterol, and high blood pressure as major risk factors for the development of coronary heart disease. Cigarette smoking acts independently of and synergistically with the other CHD risk factors to greatly increase the risk of developing coronary heart disease. The risk of developing CHD for pipe and cigar smokers is much less than it is for cigarette smokers, but more than it is for nonsmokers. In the United States, cigarette smoking can be considered the major cause of cor pulmonale since it is the most important cause of chronic non-neoplastic bronchopulmonary disease.

Autopsy studies have demonstrated that aortic and coronary atherosclerosis are more common and severe, and myocardial arteriole wall thickness is greater, in cigarette smokers than in nonsmokers.

Those who stop smoking cigarettes experience a decreased risk of death from coronary heart disease compared to that of continuing smokers.

Experimental studies in humans and animals suggest that cigarette smoking may contribute to the development of CHD through the action of several independent or complementary mechanisms: the formation of significant levels of carboxyhemoglobin, the release of catecholamines, inadequate myocardial oxygenation which may result from a number of mechanisms, and an increase in platelet adhesiveness which may contribute to acute thrombus formation. There is evidence that cigarette smoking may accelerate the pathophysiological changes of preexisting coronary heart disease and therefore contributes to sudden death from CHD.

Recently published epidemiological, autopsy, and experimental investigations have added to the understanding of the association between smoking and cardiovascular diseases.

62. U.S. PUBLIC HEALTH SERVICE. The Health Consequences of Smoki... A Public Health Service Review: 1967. U.S. Department of Health, Education, and Welfare. Washington, Public Health Service Publication No. 1696, Revised January 1969. 227 pp.

63. U.S. PUBLIC HEALTH SERVICE. The Health Consequences of Smoking. 1968 Supplement to the 1967 Public Health Service Review. U.S. Department of Health, Education, and Welfare. Washington, Public Health Service Publication 1696, 1968. 117 pp.

64. U.S. PUBLIC HEALTH SERVICE. The Health Consequences of Smoking. 1969 Supplement to the 1967 Public Health Service Review. U.S. Department of Health, Education, and Welfare. Washington, Public Health Service Publication 1696-2, 1969. 98 pp.

65. U.S. PUBLIC HEALTH SERVICE. The Health Consequences of Smoking. A Report of the Surgeon General: 1971. U.S. Department of Health, Education, and Welfare. Washington, DHEW Publication No. (HSM) 71-7513, 1971. 458 pp.

66. U.S. PUBLIC HEALTH SERVICE. The Health Consequences of Smoki... A Report of the Surgeon General: 1972. U.S. Department of Health, Education, and Welfare. Washington, DHEW Publication No. (HSM) 72-6516, 1972. 158 pp.

67. U.S. PUBLIC HEALTH SERVICE. Smoking and Health. Report of the Advisory Committee to the Surgeon General of the Public Health Service. Washington, U.S. Department of Health, Education, and Welfare, Public Health Service Publication No. 1103, 1964. 35...

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CORONARY HEART DISEASE

Epidemiological Studies

Smoking and Certain Risk Factors

A prospective epidemiological study of the factors associated with cardiovascular diseases was conducted among the 4,847 white and 2,434 black men and women of Evans County, Georgia *(23)*. The investigation was initiated with a private census and preliminary examinations beginning in 1960. Follow-up examinations were conducted after seven years. Cassel *(13)* reported that high blood pressure, elevated serum cholesterol, and cigarette smoking were major risk factors for the development of coronary heart disease. Increased body weight, an elevated hematocrit, and ECG abnormalities were additional factors that were associated with elevated CHD rates. A significant finding of this study was the very low prevalence and incidence of coronary heart disease (myocardial infarction and angina pectoris) in black men. The age-adjusted prevalence rates among black men were only half those of white men. The study showed that blacks were affected by the various risk factors for CHD in a similar fashion to whites but at a lower level of disease. This appeared to be true for any level or any risk factor or any combination of risk factors. Greater physical activity of blacks as compared to whites appeared to account for part of the observed differences in rates.

In this study, subjects were classified on the basis of their smoking history at enrollment and both current smokers and ex-smokers were considered smokers. Both black and white male smokers had a higher incidence of CHD than did nonsmokers, but white males had a higher incidence than blacks whether they were smokers or not. The age-adjusted incidence rate for white nonsmokers was 52.7 per thousand compared to 9.8 per thousand for black nonsmokers. White smokers had an incidence of 101, whereas the rate in black smokers was only 32.5. The prevalence of CHD increased with the number of cigarettes smoked per day in both groups.

The combined effect of body weight and cigarette smoking on the incidence of CHD was also examined *(25)*. The "Quetelet index"[1] was used to determine relative weight. The risk of developing CHD did not change with increases in relative weight among nonsmokers, but smokers experienced a substantial risk of developing CHD with increases in weight (figure 1).

The relationship of smoking to occupation and CHD was examined *(14)*. Farmers who performed sustained physical activity had lower rates of CHD than nonfarmers. Figure 2 shows that, while smoking increased the risk of CHD in both farmers and nonfarmers, farmers had lower rates than nonfarmers whether or not they smoked.

[1] Quetelet index = $\frac{\text{weight}}{\text{height}^2} \times 100$

23. HAMES, C. G. Introduction. (Evans County Cardiovascular and Cerebrovascular Epidemiologic Study.) Archives of Internal Medi 128(6): 883-886, December 1971.

13. CASSEL, J. C. Summary of major findings of the Evans County cardiovascular studies. Archives of Internal Medicine 128(6 887-889, December 1971.

25. HEYDEN, S., CASSEL, J. C., BARTEL, A., TYROLER, H. A., HAMES, CORNONI, J. C. Body weight and cigarette smoking as risk f Archives of Internal Medicine 128(6): 915-919, December 197

14. CASSEL, J. C., HEYDEN, S., BARTEL, A. G., KAPLAN, B. H., TYROLER, H. A., CORNONI, J. C., HAMES, C. G. Occupation and physical activity and coronary heart disease. Archives of Internal Medi 128(6): 920-926, December 1971.

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Occupation and Smoking. This paragraph implies that smoking is a more important risk factor than physical activity. The cited reference (14) Cassel et al. summarizes the epidemiologic investigation on the importance of physical activity in determining the incidence of coronary heart disease. The authors concluded that the differences in proportion of smokers was not sufficient to account for the prevalence of coronary heart disease.

> In contrast to these biological risk factors, there were sizable differences in the proportion smoking cigarettes, with fewer farmers smoking at each age than nonfarmers (Table 3). Accordingly, before concluding that the difference in incidence between farmers and nonfarmers was due to the physical activity involved in farming, the effect of cigarette smoking in farmers and nonfarmers had to be examined.
>
> From Table 4 and Fig 2 it can be seen that, while smoking increased the risk of CHD in both farmers and nonfarmers, farmers had lower rates than nonfarmers whether they smoked or not. The lower rates in farmers must, therefore, be due to some factors other than cigarette smoking.

Table 4.—Incidence of CHD* (1950-1962 to 1957-1969) in White Men, Farmers and Nonfarmers, by Age and Cigarette Smoking Status

1960 Cigarette Smoking	1960 Age, Yr	Farmers (1950 Occupation) No.	Cases	Rate	Nonfarmers (1960 Occupation) No.	Cases	Rate
Smokers and exsmokers	40-44	16	0	...	46	5	104
	45-54	59	4	68	122	11	90
	55-64	35	3	86	52	13	250
	65-74	11	4	364	33	8	242
	75+	2	0	...	3	2	667
	All ages	125	11	88	258	39	157
	Age-adjusted rate			93.7			158.2
Nonsmokers	40-44	12	0	...	13	0	...
	45-54	32	1	31	35	3	86
	55-64	40	3	75	27	1	37
	65-74	32	4	125	14	5	357
	75+	0	0	...	1	0	...
	All ages	116	8	69	90	9	100.0
	Age-adjusted rate			59.6			96.3
Unknown	40-44	7	0	...	11	4	364
	45-54	0	0	...	1	0	...
	55-64	1	0	...	0	0	...
	65-74	0	0	...	0	0	...
	75+	0	0	...	0	0	...
	All ages	8	0	...	12	4	333
	Age-adjusted rate			0			478

* Coronary heart disease.

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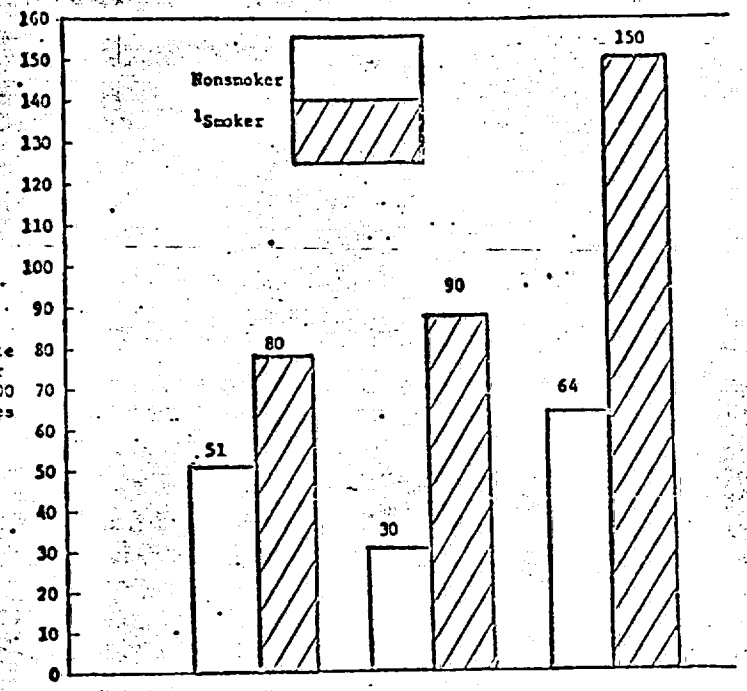

[3]Distribution by weight	Lower third (lean)		Middle third		Upper third (obese)	
Number	90	183	99	161	127	119
Cases	5	15	3	14	16	9

[1]Smokers excluding ex-smokers.
[2]87 months follow-up period.
[3]Based on Quetelet index.

Figure 1.--Age-adjusted incidence rates of CHD by [3]body weight and [1]cigarette smoking (white males).

SOURCE: Heyden, S., et al. *(26)*.

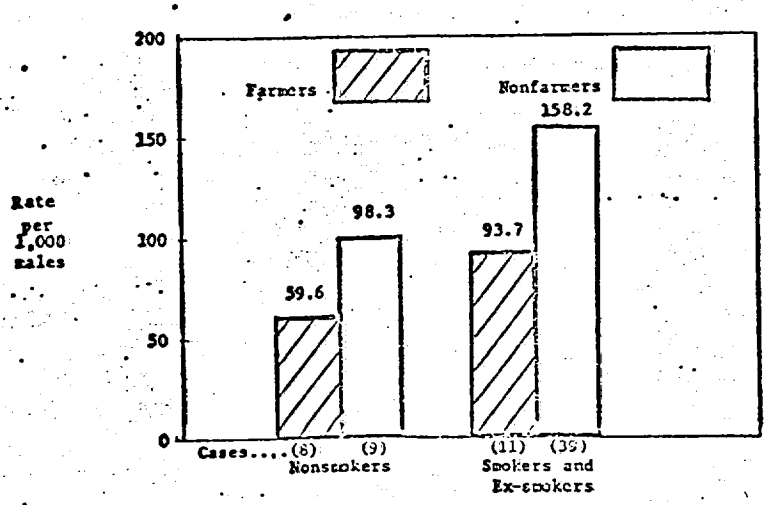

Figure 2.--Age-adjusted incidence rates of CHD comparing farmers who smoke cigarettes with nonsmoking farmers.

SOURCE: Cassel, J. C., et al. *(14)*.

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Hirayama (27) reported 5-year follow-up data on smoking in relation to death rates from a large prospective epidemiological study of 265,118 men and women in Japan. This investigation was the first of its kind to be conducted in an Asian population. During the follow-up period, 11,058 deaths occurred during 1,269,392 person years of observation. Male and female cigarette smokers experienced higher mortality rates from arteriosclerotic heart disease than did nonsmokers. Among cigarette smokers, the mortality ratios for arteriosclerotic heart disease were 1.56 ($P < .001$) for men and 1.44 ($P < .05$) for women. Dose-response relationships were found for both men and women as measured by the number of cigarettes smoked per day and age at initiation of smoking (figure 3).

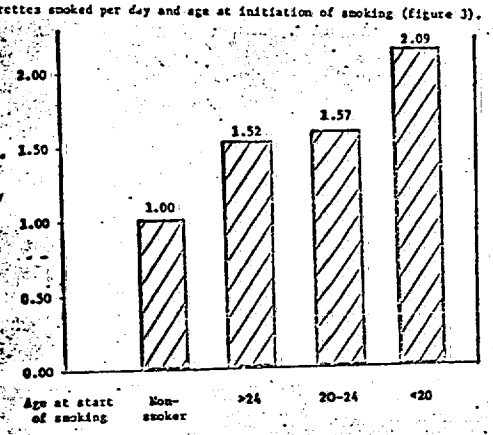

Figure 3.—Standardized mortality ratios for arteriosclerotic heart disease for males and females by age at initiation of cigarette smoking (Prospective study 1966-1970).

SOURCE: Hirayama, T. (27).

Gordon, et al. (22, 57), in a further analysis of the Framingham data, considered both by univariate and multivariate analysis the relation of certain key characteristics to the development of coronary heart disease. The characteristics were: high blood pressure, elevated serum cholesterol, cigarette smoking, left ventricular hypertrophy diagnosed by electrocardiogram, and glucose intolerance. Cigarette smoking emerged as one of the important risk factors for the development of coronary heart disease. There was a strong association between cigarette smoking and CHD other than angina pectoris, particularly among young male and female smokers. The relative role of cigarette smoking as a risk factor was emphasized by multivariate analysis. Cigarette smoking was not as strongly related to CHD in women as it was in men. This may have been in part due to the fact that there are fewer heavy smokers among women, and women tend to inhale smoke less than men.

HIRAYAMA, T. Smoking in relation to the death rates of 265,... men and women in Japan. A report of five years of follow-... Presented at the American Cancer Society's Fourteenth Scie... Writers' Seminar, Clearwater Beach, Florida, March 27, 197... 15 pp.

22. GORDON, T., SORLIE, P., KANNEL, W. B. Section 24. Coronary heart disease, atherothrombotic brain infarction, intermittent claudication—a multivariate analysis of some factors related to their incidence: The Framingham Study, 16-year follow-up. IN: Kannel, W. B., Gordon, T. (Editors). The Framingham Study. An Epidemiological Investigation of Cardiovascular Disease. May 1971. 42 pp.

57. SHURTLEFF, D. Section 26. Some characteristics related to the incidence of cardiovascular disease and death: Framingham Study, 16-year follow-up. IN: Kannel, W. B., Gordon, T. (Editors). The Framingham Study. An Epidemiological Investigation of Cardiovascular Disease. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, Washington, D. C., December 1970. 35 pp.

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Kagan, et al. *(31)* reported preliminary findings from the Honolulu Heart Study. The effect of migration on dietary patterns and the incidence of cardiovascular diseases in a cohort of men of Japanese ancestry born between 1900 and 1919, who were residents of Oahu in 1965, was examined in this prospective study. During the two years of follow-up, 101 men developed CHD in the population of 8,006 men initially examined. A significant relationship to CHD was found for the following risk factors: cigarette smoking, elevated systolic and diastolic blood pressure, increased serum cholesterol, triglycerides or uric acid, and various measures of obesity.

Using data from the International Cooperative Study on Cardiovascular Epidemiology, Keys, et al. *(34)* calculated the probabilities for men aged 40 to 59 to develop coronary heart disease in five years. The authors noted "...that the relative CHD risk of different men within a given population is well predicted from the results of the multivariate analysis of the experience of men in other far-distant populations differing in socioeconomic circumstances, language, and ethnic background." Although the CHD incidence rate of European men was about half that of the Americans, the fact still remained that investigation of the four variables (cigarette smoking, age, systolic blood pressure, and cholesterol) was sufficient to identify men whose likelihood of dying of CHD or having a definite myocardial infarction within five years was greatly above the average.

Punsar *(51)* reported 10-year follow-up data on the cohort of men in Finland who were part of the 7-country study of coronary heart disease, confirming that cigarette smoking was a major risk factor for CHD. The authors reported a 1.7-fold increase in CHD mortality among cigarette smokers. They estimated that 1,700 excess CHD deaths occur each year among cigarette smoking men in Finland.

Kozarevic, et al. *(38)* reported the results of the initial prevalence survey and the 2-year incidence data from the Yugoslavian study of cardiovascular disease. A total of 11,121 men between the ages of 35 and 62 were examined in the towns of Tuzla and Remetinec. Criteria for the diagnosis of CHD were based on objective electrocardiographic findings of myocardial infarction, left bundle branch block, or sudden death. A very low prevalence of myocardial infarction was initially found, and only 36 new cases of CHD developed over the 2-year period. The subjects who developed CHD smoked cigarettes at about the same level as the total study population. The annual average incidence rate of acute coronary heart disease was about 1.6 per 1,000 among both the smokers and nonsmokers. The CHD incidence rates found in this Yugoslavian study are appreciably below those found in the United States.

Comstock *(16)* examined the association between water hardness, various other environmental factors including cigarette smoking, and death from CHD. A total of 189 deaths from CHD occurred in the population of Washington County, Maryland, in the 3-year period following a census in 1963. For each case, two controls were randomly selected from the census lists and matched for race, sex, and year of birth. The relative risk of CHD for all smokers was 1.3 compared to nonsmokers ($P < .05$). This relative risk among cigarette smokers was dose-related; persons smoking more than two packs a day had the highest risk of CHD.

31. KAGAN, A., RHOADS, G. G., ZEEGEN, P. D., NICHAMAN, M. Z. Coronary heart disease among men of Japanese ancestry in Hawaii. The Honolulu Heart Study. Israel Journal of Medical Sciences 7(12): 1573-1577, December 1971.

34. KEYS, A., ARAVANIS, C., BLACKBURN, H., VAN BUCHEM, F. S. P., BUZINA, R., DJORDJEVIC, B. S., FIDANZA, F., KARVONEN, M. J., MENOTTI, A., PUDDU, V., TAYLOR, H. L. Probability of middle-aged men developing coronary heart disease in five years. Circulation 45(4): 815-828, April 1972.

51. PUNSAR, S. Tupakointi ja sepelvaltiotauti. (Cigarette smoking and coronary heart disease.) Suomen Lääkärilehti 26(1/2): 27-32, January 9, 1971.

38. KOZAREVIC, D., PERC, B., DAWBER, T. R., KANN, H. A., ZUKEL, W. J. Prevalence and incidence of coronary disease in a population study. The Yugoslavia Cardiovascular Disease Study. Journal of Chronic Diseases 24(7/8): 495-505, September 1971.

16. COMSTOCK, G. W. Fatal arteriosclerotic heart disease, water hardness at home, and socioeconomic characteristics. American Journal of Epidemiology 94(1): 1-10, July 1971.

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Environmental Factors . The epidemiologic studies cited in this page are not described completely. For example, (16) Comstock reported other factors which influence the risk of coronary heart disease. Deaths from heart disease were more common among persons of lower socioeconomic status and among persons who attended church infrequently. As a matter of fact, the correlation with church attendance was better that with cigarette smoking. The illustration on risk factors, Comment and Summary are as follows:

Comstock, G. W. (Training Center for Public Health Research, Johns Hopkins School of Hygiene and Public Health, Box 2067, Hagerstown, Md. 21740). Fatal arteriosclerotic heart disease, water hardness at home, and socioeconomic characteristics. *Amer J Epidem* 94: 1–10, 1971.—Several reports have indicated an inverse correlation between the hardness of community water supplies and deaths from arteriosclerotic and degenerative heart disease. An unusual opportunity to look at this association in more detail arose in Washington County, Maryland. Drinking water sources there vary markedly in hardness, and a private census in 1963 made it possible to match cases and controls from the same defined population and to study a number of socioeconomic characteristics. During the next three years, there were 189 deaths attributed to arteriosclerotic and degenerative heart disease among white males aged 45 to 64 who could be identified in the census. For each case, 2 controls were randomly selected from the census lists and matched for race, sex and year of birth. Water samples were collected from the residences of cases and controls and examined for total hardness. No significant association of arteriosclerotic and degenerative heart disease deaths could be found with water hardness. Deaths from these causes were more common among persons of lower socioeconomic status, among cigarette smokers, and among persons who attended church infrequently. Although water hardness is not likely to be a real risk factor for cardiovascular disease, the role of trace elements in home drinking water supplies should be investigated.

arteriosclerosis; coronary disease; epidemiology; heart diseases; religion; water

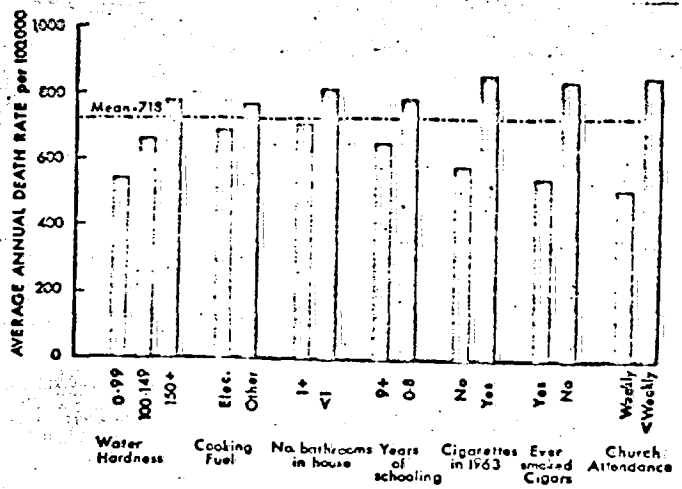

FIGURE 1. Average annual death rates from ASDHD for white males, 45–64 years, Washington County, Maryland, by hardness of home drinking water and selected socioeconomic and personal characteristics. (Each rate adjusted for all other selected characteristics and for age.)

A surprising finding was the strong negative association of frequency of religious attendance with fatal arteriosclerotic heart disease. It is premature to speculate on the meaning of this association other than to note that it is obvious that regular church attenders differ in many ways from those who rarely or never go to church. It is also possible that church attendance may produce a favorable psychic or emotional response. Because frequency of attendance is an aspect of religious experience that is very easily determined, it is hoped that future investigations will include information on church attendance to confirm or deny its importance as a risk factor for arteriosclerotic heart disease. If confirmed, the implications of this finding raise intriguing questions for future research.

The implications of identifying a water factor in the causation of arteriosclerotic cardiovascular disease are quite different. If some component of drinking water is causing disease, it can almost certainly be reduced or removed. If the water factor is a deficiency of some kind, this can be remedied. In either case, preventive treatment could quickly benefit large segments of the population. It is this possibility of an effective mass attack on a major health problem that makes further exploration for a water factor a matter of high priority.

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Casciu, et al. *(12)* reported the prevalence of cardiovascular diseases among 4,668 miners on Sardinia. Smoking and drinking habits, blood pressure, and heart rates were recorded. Smokers had higher rates of CHD than nonsmokers, and a dose-response was noted with the number of cigarettes smoked per day. The prevalence of myocardial infarction was 0.9 percent for nonsmokers, 1.62 percent for smokers of 10 or less cigarettes, 2.34 percent for smokers of 11 to 20 cigarettes, 4.8 percent for smokers of 20 or more cigarettes a day, and 1.42 percent for cigar or pipe smokers. When cigarette smokers were grouped by alcohol consumption, no significant difference was found in the prevalence of myocardial infarction between drinkers and nondrinkers.

Kornitzer, et al. *(35, 36, 37)* examined the prevalence of CHD in 566 male bank employees aged 40 to 59 in Brussels. They determined an individual's smoking history, blood lipids, ECG, peak flow rates, relative weight, skinfold thickness, and blood pressure. The prevalence of possible CHD as determined by ECG and CHD history was 7.1 percent in nonsmokers, 11.6 percent in cigarette smokers who inhaled, 6.9 percent in cigarette smokers who did not inhale, 10.6 percent in smokers of pipes and cigars, and 15.5 percent in the ex-smokers. Among the various risk factors examined, the strongest association was found for elevations in the serum cholesterol and the other blood lipids examined. Weaker associations were found for increased relative weight, high blood pressure, and tobacco use.

Agnese, et al. *(2)* examined 265 patients in Italy aged 20 to 65 years who had myocardial ischemia. Patients were matched with an equal number of controls by age. A number of risk factors for CHD were measured in both groups. Cigarette smoking and elevated serum cholesterol were identified as major risk factors for CHD, particularly for individuals under the age of 50.

Boudik *(10)* found the prevalence of myocardial infarction to be significantly ($P < .001$) higher in cigarette smokers than in nonsmokers in a population of 8,292 Czechoslovakian men between the ages of 52 and 67.

Storch, et al. *(60)*, Estandia Cano, et al. *(17)*, and Jakuszewska *(30)*, in studies in Germany, Mexico, and Poland of CHD in individuals under the age of 40, reported that cigarette smoking was the dominant factor in the development of CHD in these patients.

Colovchiner *(21)* found cigarette smoking to be a significant factor in the development of myocardial infarction in a study of 530 patients with CHD in Leningrad hospitals.

Three studies without control groups from New Zealand *(59)*, Nepal *(47)*, and India *(58)* reviewed the prevalence of various risk factors, including cigarette smoking in populations with documented CHD.

12. CASCIU, G., MARRACCINI, L., ZEDDA, S., CARTA, G., FULGILE..., G. Sulla frequenza delle cardiovasculopatie tra gli operai dell'industria estrattiva della sardegna. Nota II: Incidenza in rapporto all'abitudine al fumo e all'alcool. (On the incidence of cardiovascular disease among the workers of the mining industry of Sardinia. Second communication: Incidence in relation to habitual smoking and consumption of alcohol.) Rassegna Medica Sarda 71(Supplement 1): 191-200, 1968.

35. KORNITZER, M., DEMEESTER, M., DELCOURT, R., BERNARD, R. Cardiopathies ischémiques dans une population d'employés de Bruxelles. Etude de la prévalence des cardiopathies ischémiques en fonction de la classe socio-économique. (Ischemic heart disease in a Brussels bank clerk population. Study of the prevalence of ischemic heart diseases as a function of socioeconomic class.) Revue d'Epidemiol Medecine Sociale et Sante Publique 19(7): 599-612, October-November 1971.

36. KORNITZER, M., DEMEESTER, M., DELCOURT, R., GOOSSENS, A., BERNARD, R. Enquête cardio-vasculaire prospective dans une population sélectionnée: resultats de l'enquête initiale. (Prospective cardiovascular studies in a selected population. Results of the initial study.) Acta Cardiologica 26: 265-343, 1971.

37. KORNITZER, M., DEMEESTER, M., DENOLIN, H. Enquête dans une populati d'employes. Relation des habitudes tabagiques avec d'autres parametres. (Investigation of a white-collar population. Relatio of tobacco habits to other parameters.) Bruxelles Medical 51(10): 687-691, October 1971.

2. AGNESE, G., CANEPA, R., LA ROCCA, M. Eta e valore di alcuni indic per la discriminazione fra soggetti normali ed ischemici. (Age and value of several indices for discrimination in normal and ischemic subjects.) Giornale di Igiene e Medicina Preventiva 11(3): 140-151, July-September 1970.

10. BOUDIK, F. Srdecni infarkt a koureni. (Myocardial infarction and smoking.) Casopis Lekaru Ceskych 110(25): 614-620, July 25, 197

60. STORCH, H., ENGELMANN, L., KOHLER, H. Der Herzinfarkt im jüngere Lebensalter. (Myocardial infarct in young people.) Deutsche Gesundheitswesen 26(34): 1593-1600. August 1971.

17. ESTANDIA CANO, A., ESQUIVEL AVILA, J., MALO CAMACHO, R., PEREZ SANTANDER, S., LEON MONTANEZ, E. Infarto juvenil del miocardio (Myocardial infarction in the younger age groups.) Archivos d Instituto de Cardiologia de Mexico 41(2): 137-150, March-April

30. JAKUSZEWSKA, R. Zawal serca u osob mlodych. (Myocardial infarc in young subjects.) Wiadomosci Lekarskie 22(19): 1749-1752, October 1, 1969.

21. COLOVCHINER, I. Y. Nekotoryye sotsial'nyye faktory zabolevaye infarktom miokarda. (Some social factors in the incidence of myocardial infarct.) Zdravookhraneniie Rossiiskoi Federatsii 15(9): 12-14, 1971.

59. SMYTH, A. J., APPY, H., LANGLEY, R. B. An epidemiological surv of ischemic heart disease. New Zealand Medical Journal 71(4 284-286, May 1970.

47. PANDEY, M. R. Myocardial infarction in Nepal. Indian Heart J 22(2): 73-82, April 1970.

58. SINGH, A. P., SINGH, S. P. Coronary heart disease—some epidemiolo clinical and electrocardiographic observations. Journal of the Association of Physicians of India 19(9): 629-635, September 1971.

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Blood Lipids

In most of the following studies where the effect of cigarette smoking on blood lipids was examined, there was no control for dietary factors that may independently affect serum lipid levels. Schwartz, et al. *(56)* examined serum lipids in relation to smoking habits and relative weight in 7,972 male employees of the Parisian Civil Service in the city of Paris. Cigarette smoking was associated with a slight but significant (P <.001) increase in serum cholesterol. The authors found a positive correlation between increased relative weight and serum cholesterol levels, and a negative correlation between relative weight and smoking habits. These factors would operate in such a way as to reduce the apparent effect of cigarette smoking on the cholesterol levels. After controlling for relative weight, however, the investigators found a significant (P <.001) positive relationship between smoking and serum cholesterol.

56. SCHWARTZ, D., RICHARD, J. L., LELLOUCH, J., CLAUDE, J. R. Serum lipids, smoking and body build. Study of 7,972 actively employ males. Revue Europeenne d'Etudes Cliniques et Biologiques 16: 529-536, 1971.

In a study of various factors in relation to the mean serum cholesterol, Pincherle *(48)* examined the following parameters: blood pressure, height, weight, and skinfold thickness, X-ray findings of the chest and abdomen, the electrocardiogram, and smoking history. Ten thousand British business executives between the ages of 25 and 65 were examined. A significant association was found between elevated serum cholesterol, obesity, elevated systolic blood pressure, inadequate exercise, radiographic evidence of arterial calcification of the iliac arteries, and certain other factors. The increase observed in mean serum cholesterol with increasing number of cigarettes smoked was not statistically significant.

48. PINCHERLE, G. Factors affecting the mean serum cholesterol. Jou of Chronic Diseases 24(5): 289-297, August 1971.

Romslo *(53)* studied the distribution of serum lipids in 324 Norwegian military recruits. Cigarette smokers had a small but insignificant increase in serum triglycerides. No elevation was found for serum cholesterol. The subjects were young, and most smokers had only smoked for a few years.

53. ROMSLO, I. Distribution of serum lipids in Norwegian recruits. Acta Medica Scandinavica 190(5): 401-406, November 1971.

Burney and Enslein *(11)* investigated changes in clinical laboratory tests as related to aging and smoking in a 5-year study of 502 healthy male veterans. It was found that five variables were needed to predict age-related changes in those over 50. These were: fasting blood glucose, 2-hour post-glucose blood sugar, total serum protein, hemoglobin, and cholesterol esters. No significant differences in the laboratory data between smoking and nonsmoking subgroups were found.

11. BURNEY, S. W., ENSLEIN, K. Investigation of changes in clinical laboratory tests related to aging and smoking. Aging and Human Development 3(1): 95-101, February 1972.

Vlaicu, et al. *(70)* examined the interaction of cigarette smoking with blood pressure and serum lipids in 100 patients with angina pectoris who were between the ages of 40 and 59. Half the patients were smokers using more than 25 cigarettes a day. The smokers had lower serum lipids and lower blood pressure than the 50 nonsmoking patients with angina pectoris.

70. VLAICU, R., MACAVEI, E., PATIU, I. Studiu transversal ("cross-sectional") al presiunii arteriale si al lipidelor serice la coronarieni fumatori si nefumatori. (Cross-sectional study of arterial pressure and serum lipids in coronary smokers and nonsmokers.) Medicina Interna 23(8): 925-930, August 1971.

Mitwrzynska-Stryjecka, et al. *(43)* found that cigarette smoking immediately following a fatty meal did not significantly alter the serum free fatty acid, esterified fatty acid, cholesterol, or plasma turbidity levels over control values.

43. MITURZYNSKA-STRYJECKA, M., WIDOMSKA-CZEKAJSKA, T., RUDNIEWSKA, Z. Wplyw palenia papierosow na lipemie po posilku tluszczowym. (The effect of acute experiment of cigarette smoking on lipaemia following fat meal.) Polski Tygodnik Lekarski 25(7): 251-253, February 16, 1970.

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Smoking and Blood Lipids. This citation is inserted among reports dealing on normal individuals. The observations of (70) Vlaicu et al. were made on 100 patients with angina pectoris. It is important because the study indicates that in patients, smoking does not modify serum lipid levels. The Summary is as follows:

SUMMARY

R. Vlaicu, Emilia Macavei, I. Papiu — CROSS-SECTIONAL STUDY OF ARTERIAL PRESSURE AND SERUM LIPIDS IN CORONARY SMOKERS AND NON-SMOKERS

Arterial pressure, cholesterol, total lipemia and serum beta-lipoproteins were studied in 100 patients with painful ischemic cardiopathy, aged 40 to 59 years, of whom 50 smoking over 25 cigarettes a day and 50 non-smokers.

The statistical difference between the two groups was significant, arterial pressure and blood lipids presenting higher values in the non-smokers, than in smokers.

It is considered that in coronary smokers, in the absence of other risk factors (high arterial pressure and serum lipid levels), smoking is the main risk factor. In the production of coronaropathy, smoking does not appear to act by modifying blood pressure and/or serum lipid levels.

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Ciampolini, et al. *(15)* examined the effects of cigarette smoking on blood lipid values in 10 healthy volunteers between the ages of 20 and 40. Cigarette smoking resulted in a prompt rise in free fatty acids and a delayed rise in serum triglycerides.

The relationship between cigarette smoking and changes in various serum lipid levels has not been clearly determined. Studies in this area continue to present conflicting results.

15. CIAMPOLINI, E., DRINGOLI, R., RAVAIOLI, P. Azione del fumo di sigarette su alcuni parametri del ricambio lipidico. (Action of cigarette smoking on several parameters of lipid metabolism.) Atti dell'Accademia dei Fisiocritici in Siena; Sezione Medico-Fisica 17: 474-480, 1968.

Electrocardiogram

Wysokinski *(76)* examined the effect of smoking on certain parameters of cardiovascular function in 100 healthy nonsmokers and 100 healthy smokers who were military recruits 19 to 25 years of age in Poland. Significant prolongation of the QRS interval ($P < .001$), flattening of the T wave, and ST segment depression following exercise were seen more frequently in the smokers than in the nonsmokers.

76. WYSOKINSKI, Z. Effects of tobacco smoking on certain parameters reflecting the condition of the circulatory system at rest and during exercise. Polish Medical Science and History Bulletin 14(2): 73-76, April 1971.

Van Buchem, et al. *(69)* examined the occurrence and significance of extrasystoles and conduction disorders in 760 healthy Dutch men between the ages of 40 and 67 who were followed for seven years. The presence of extrasystoles was not correlated with cigarette smoking or elevated serum cholesterol and was not associated with the development of CHD over the 7-year period.

69. VAN BUCHEM, F. S. P., DRION, E., WIGBOUT, H., BOSSCHIETER, E., FRIPA, J. R. Het voorkomen en de betekenis van extrasystolen en geleidingsstoornissen. Een 7-jarige longitudinale studie (I). (The occurrence and significance of extrasystoles and conduction disorders. A longitudinal study over 7 years (I).) Nederlands Tijdschrift voor Geneeskunde 114(7): 281-286, February 14, 1970.

Kattus, et al. *(33)* tested 314 healthy males 23 to 82 years of age for ischemic ST segment depression on the ECG during or after sub-maximal exercise. The abnormal ST segment depression identified in 30 subjects was correlated significantly with elevated serum cholesterol, abnormal resting ECG, and a history of cardiac symptoms but not with smoking, high blood pressure, physical inactivity, or family history of coronary disease.

33. KATTUS, A. A., JORGENSEN, C. R., WORDEN, R. E., ALVARO, A. B. ST-segment depression with near-maximal exercise in detection of preclinical coronary heart disease. Circulation 44(4): 585-595, October 1971.

Van Buchem, et al. *(68)* found no significant association between cigarette smoking and ischemic ST segment depression on ECG in 120 apparently healthy men who demonstrated this abnormality among a population of 760 men 50 to 70 years of age.

68. VAN BUCHEM, F. S. P., DRION, E., WIGBOUT, H., BOSSCHIETER, E. Het voorkomen en de betekenis van een depressie van het ST-segment in het elektrocardiogram bij mannen zonder andere verschijnselen. Een 7-jarige longitudinale studie (II). (The occurrence and the significance of a depression of the ST segment in the ECG of men free from other symptoms. A longitudinal study of 7 years (II).) Nederlands Tijdschrift voor Geneeskunde 114(8): 320-332, February 21, 1970.

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Smoking and the Electrocardiogram. One would conclude after reading this section that in some studies, smoking did not influence the ECG. Only the first study by (76) Wysokinski did something different from the others. He had subjects smoke 5 cigarettes and perform exercise. The abnormal electrocardiogram appeared as an acute effect on smoking and exercising. The Table of Results is quoted below.

The other 3 investigations were comparing the electrocardiogram of smokers and nonsmokers without smoking excessively prior to the recording. There is therefore no inconsistency in the conclusions that there is no significant association between smoking and the ischemic pattern of the electrocardiograph.

Smoking of 5 cigarettes had an evidently harmful effect on the circulatory system; the number of abnormal reactions was almost double in relation to the number of abnormal reactions in the studied subjects before smoking, the difference being statistically significant ($p < 0.01$). The harmful effect of tobacco smoking was even more evident in the group of smokers after smoking of cigarettes, as compared to the control group. These differences were highly significant statistically ($p < 0.01$).

The ECG investigation showed also a harmful effect of cigarette smoking on the circulatory system. After smoking of cigarettes at rest a statistically significant prolongation of the P wave was observed ($0.20 > p > 0.10$) and of the PQ segment ($0.30 > p > 0.20$). (Table II). The effort after smoking of cigarettes caused a statistically significant prolongation of the QRS complex ($p > 0.01$). After smoking of cigarettes before Letunov's test abnormalities of ECG appeared with flattening of T wave, depression of ST segment, more rarely with grade I atrioventricular block. These differences were statistically highly significant ($p < 0.01$), as compared with the number of abnormal ECG records in the smokers before smoking of cigarettes, as well as in the control group (10).

TABLE II

Effect of smoking on ECG

Parameter	Mean value of parameter in groups			Comparison of mean values in groups					
	Non-smokers A	Smokers		A - B		A - C		B - C	
		Before smoking B	After smoking C	Difference	Risk of error	Difference	Risk of error	Difference	Risk of error
P wave	0.0997	0.1015	0.1042	+0.0018	$0.40 > p > 0.30$	+0.0045	$0.05 > p > 0.02$	+0.0027	$0.20 > p > 0.10$
PQ segment	0.1425	0.1494	0.1537	+0.0059	$0.10 > p > 0.05$	+0.0102	$p < 0.01$	+0.0043	$0.30 > p > 0.20$
QRS complex	0.0795	0.0809	0.0758	+0.0014	$0.50 > p > 0.40$	+0.0003	$0.90 > p > 0.80$	-0.0011	$0.60 > p > 0.50$
T wave	0.1756	0.1670	0.1694	-0.0086	$0.05 > p > 0.02$	-0.0062	$0.20 > p > 0.10$	+0.0024	$0.60 > p > 0.50$

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Experimental Studies

Cigarette Smoke

Studies in Man

Summers, et al. *(61)* examined the effect of cigarette smoking on cardiac lactate metabolism in 15 patients with severe angina pectoris who had at least 75 percent obstruction in each of two or three major coronary vessels. All patients had been long-term cigarette smokers. Cigarette smoking produced increases in heart rate, systolic aortic pressure, the systolic ejection period per minute, and the tension-time index per minute, but lactate production was not induced by smoking in any patient who did not also have lactate production in the control state. In three patients with lactate abnormalities prior to smoking, inhalation of cigarette smoke sustained and slightly aggravated this condition.

61. SUMMERS, D. N., RICHMOND, S., WECHSLER, S. M. Cigarette smoke: Effects on lactate extraction in the presence of severe coronary atherosclerosis. American Heart Journal 82(4): 458-467, October 1971.

Studies in Animals

The effect of inhalation of cigarette smoke on ventricular fibrillation threshold (VFT) in normal dogs and dogs with experimentally produced acute myocardial infarction was studied by Bellet, et al. *(6)*. Mongrel dogs weighing 25 to 30 kilograms were anesthetized with sodium pentobarbital, and respiration was maintained using a Harvard ventilator attached to an endotracheal tube. In one group the electrical impulses used to precipitate ventricular fibrillation were delivered through the chest wall, and in another group the impulses were delivered directly to the heart through electrodes implanted in the myocardium. The experimental group of dogs were exposed to the smoke of three cigarettes over a 10-minute period. Each cigarette contained approximately 2 mg. of nicotine. With acute myocardial infarction, the VFT was significantly ($P < .001$) decreased, but in both the normal and myocardial infarction groups cigarette smoking resulted in a decrease in VFT that averaged 30 to 40 percent of the control value (figure 4). These findings are of interest in view of the increased incidence of sudden death observed among coronary patients who are heavy cigarette smokers *(65)*.

6. BELLET, S., DeGUZMAN, N. T., KOSTIS, J. B., ROHAN, L., FLEISCHMANN, The effect of inhalation of cigarette smoke on ventricular fibrillation threshold in normal dogs and dogs with acute myocardial infarction. American Heart Journal 83(1): 57-76, January 1972.

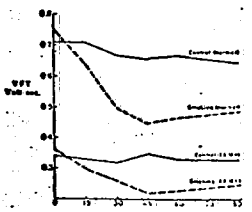

Figure 4.—The effect of cigarette smoke inhalation on the ventricular fibrillation threshold (VFT) of normal dogs and dogs with experimentally produced acute myocardial infarction (AMI).

SOURCE: Bellet, S., et al. *(6)*.

The effects of passively inhaled cigarette smoke on several measures of cardiovascular function in treadmill-exercised dogs were examined by Reece and Ball *(52)*. The experimental dogs were trained on the treadmill for approximately one year before exposure to cigarette smoke began. Each dog was passively exposed to the smoke of 36 cigarettes over a 3-hour period five days a week in a 2.2 m^3 chamber ventilated at the rate of seven exchanges per hour. The dogs were exposed to this cigarette smoke and were continued on their

52. REECE, W. O., BALL, R. A. Inhaled cigarette smoke and treadmill-exercised dogs. Archives of Environmental Health 24(4): 262-270, April 1972.

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Cigarette Smoke and Lactate Extraction. The report of (61) Summers et al. is an important one because it relates directly to the influence of cigarette smoking on patients with severe angina pectoris. It is more relevant than the observations of Aronow and Rakow discussed in page 483 (a). Lactate production of the myocardium was used by Summers as criteria for ischemia whereas exercise tolerance was used by Aronow and Rakow.

Portions of the Introduction, Discussion and Summary of (61) Summers et al. are quoted as follows:

Epidemiologic studies have demonstrated a significant relationship between cigarette smoking and obliterative vascular disease.[1] Of clinical importance is the significant relationship between cigarette smoking, myocardial infarction, and sudden death. Several studies[2-4] show an increase in deaths from coronary disease in cigarette smokers.

The objectives of this study were to determine whether the inhalation of cigarette smoke could acutely induce myocardial ischemia as reflected by abnormal myocardial lactate metabolism in patients with severe diffuse obstructive coronary artery disease, to compare this situation to the effects of catecholamine administration, and to measure some of the hemodynamic responses to the inhalation of cigarette smoke.

The absence of lactate production during smoking must be further considered. It might mean that the hemodynamic changes induced were not sufficient to cause myocardial ischemia, or that the method used was insufficiently sensitive to determine this occurrence. It would seem that the former was more likely since clinical expression of ischemia in the form of angina pectoris is not more frequently associated with smoking[5] and might be expected to be so if ischemia was produced. Another alternative would be that coronary blood flow was increased in these patients. Regan and associates[11] found no increase in coronary flow in subjects with coronary artery disease during smoking. Finally, nicotine might cause regional flow redistribution to the benefit of potentially underperfused areas. Evaluation of this possibility awaits the availability of methods for studying regional flow in the intact heart.

Summary

Fifteen patients with angiographically demonstrated severe obstructive coronary artery disease were the study subjects. Hemodynamic measurements were made before and during cigarette smoking, and metabolic evaluation was performed in these states and during isoproterenol stress. Heart rate, aortic pressure, systolic ejection and diastolic filling periods were measured. Myocardial lactate extraction was evaluated at three coronary sinus drainage sites. Despite increases in heart rate, aortic pressure, the systolic ejection period per minute, and the tension-time index per minute lactate production was not induced by smoking in any patient without lactate production in the control state. In 3 patients with lactate abnormalities prior to smoking, inhalation of cigarette smoke sustained and slightly aggravated this circumstance. Isoproterenol induced lactate production in all but 1 patient.

Cigarette smoking in a group of patients with severe obstructive coronary artery disease did not produce evidence of ischemia as determined by abnormalities in lactate extraction.

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exercise program for an additional year. Exposure to cigarette smoke was associated with cardiac enlargement, ST segment depression, and an increase in post-exercise serum lactate concentrations.

Nicotine

Studies in Man

Isaac and Rand (28) have recently described a method for the assay of plasma nicotine. An alkali flame ionization detector was used with a gas-liquid chromatograph. The test is sensitive to 1 ng./ml. of nicotine in a 2.5 ml. sample. Thirty minutes elapsed between end of one cigarette and start of next. Blood samples were taken before smoking and at 0.5, 10, and 30 minutes after the last puff of each cigarette. Plasma nicotine levels increased rapidly during cigarette smoking (figure 5). The post-smoking decay curve consisted of two components: an initial rapid phase which may be due to the uptake of nicotine from the blood by various tissues, and a slower phase which may represent metabolism and excretion of nicotine. Some accumulation of plasma nicotine occurred during a day of smoking, but the background level never approached the peaks attained during and immediately following active cigarette smoking. The rate of elimination was rapid enough to prevent any appreciable accumulation of nicotine from one day to the next. The development of sensitive tests of plasma nicotine levels will allow a greater understanding of various dynamics of smoking. Inhalation patterns can be objectively measured, and the role of nicotine in habituation to cigarettes can be evaluated.

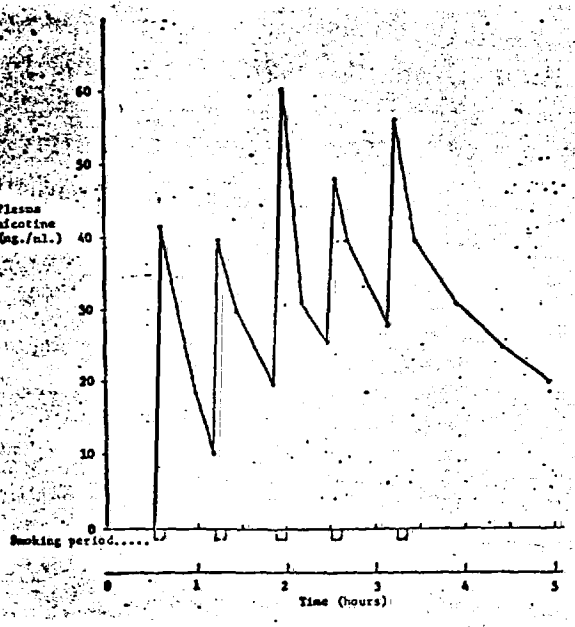

Figure 5.--Effects of smoking five consecutive cigarettes on plasma nicotine concentration.

SOURCE: Isaac, P. F., Rand, M. J. (28).

28. ISAAC, P. F., RAND, M. J. Cigarette smoking and plasma levels of nicotine. Nature 236(5345): 302-310, April 7, 1972.

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Studies in Animals

The effect of nicotine on regional blood flow in the canine heart was examined by Mathes and Rival *(41)*. The effects of nicotine were examined in normal hearts and after partial coronary artery occlusion. Under normal circumstances, as well as after infusion of nicotine in normal hearts, the subendocardial portion of the myocardium had a 9.5 percent greater capillary flow than the subepicardial fraction. Partial ligation of the coronary arteries resulted in a 22.8 percent reduction in left ventricular blood flow; however, the subendocardial portion remained 8.6 percent higher than in the epicardium. After coronary artery ligation, an infusion of nicotine resulted in a significant ($P < .001$) reduction in the capillary flow of the inner portion of the myocardium relative to the outer part.

41. MATHES, P., RIVAL, J. The effect of nicotine on regional blood flow in the canine heart. Proceedings of the Society for Experimental Biology and Medicine 138(1): 361-364, October 1971.

Bhagat, et al. *(7)* examined the effect of cigarette smoking on the cardiovascular system of dogs. Various pharmacological agents, e.g., tyramine hydrochloride, propranolol, and chlorisondamine, were used to modify the evoked response to tobacco smoke in order to clarify the mechanisms producing the observed effects. The authors concluded that the more important actions of nicotine include a stimulation of sympathetic ganglia and the adrenal medulla and the release of catecholamines from sympathetic nerve endings and chromaffin tissue.

7. BHAGAT, B., RUEHL, A., RIO, P., RAMA, M. W., HUGHES, M. J. Effect of cigarette smoke on the cardiovascular system in dogs. Proceedings of the Society for Experimental Biology and Medicine 137(3): 969-972, July 1971.

Bing, Hellberg, and associates *(8, 25)* studied the microcirculation of the left atrium of anesthetized cats by direct visualization using high speed cinematography. Nicotine injections produced a slight but insignificant increase in red cell velocity in the capillary circulation during both systole and diastole.

8. BING, R. J., WAYLAND, H., RICKART, A., HELLBERG, K. Studies on the coronary microcirculation by direct visualization. Giornale Italiano di Cardiologia 1: 401-408, September-October 1971.

25. ——, K., WAYLAND, H., RICKART, A. L., BING, R. J. Studies on the coronary microcirculation by direct visualization. American Journal of Cardiology 29: 593-597, May 1972.

The effects of nicotine on the biosynthesis of various lipid fractions in the aorta of dogs were studied by Kupke *(40)*. After nicotine administration, significant reduction occurred in the formation of free (^{14}C)-sterols, while elevated levels of unesterified fatty acids were formed in the media and intima of these *in vitro* specimens. The author suggested that nicotine may impair oxidative enzyme systems possibly by damaging the mitochondrial structures, thereby leading to lipid accumulation in the aorta.

40. KUPKE, I. R. Biosynthesis of lipids in perfused dog aorta and coronary artery. II. Incorporation of (2-^{14}C) acetate into lipids of two aortic layers and of the coronary artery under the influence of nicotine. Journal of Molecular and Cellular Cardiology 4(1): 27-38, February 1972.

Schievelbein and Eberhardt *(54)* reviewed the cardiovascular actions of nicotine and smoking.

54. SCHIEVELBEIN, H., EBERHARDT, R. Cardiovascular actions of nicotine and smoking. Journal of the National Cancer Institute 48(6): 1785-1794, June 1972.

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Nicotine on Regional Coronary Blood Flow. The observations of (41) Mathes and Rival need further comments to place them in proper perspective. The reduction in blood flow in the subendocardial portion is not unique for nicotine but for drugs including catecholamines that influence intraventricular pressure.

Nicotine was administered by infusion large enough to cause a rise in blood pressure of from 119/86 to 154/108. This degree of pressor effect is not encountered in ordinary smoking. Portions of the Introduction and Comments are quoted below:

> Nicotine administration elicits a number of complex cardiovascular responses the precise mechanisms of which are not clearly understood. The hemodynamic effects, which have been attributed chiefly to the release of catecholamines, consist mainly of an increase in arterial pressure, heart rate, and stroke work and a resultant increase in coronary blood flow (1–3). The susceptibility of regional myocardial blood flow to changes in ventricular pressure and coronary perfusion has been demonstrated in this laboratory (4), as well as by other investigators (5–7). The present investigations were aimed at studying the effect of nicotine on the regional distribution of capillary flow in the canine heart. The perfusion of the subendocardial portion of the left ventricle was examined because this area has been shown to be especially vulnerable to changes in coronary perfusion and arterial pressure (4, 6, 7). Coronary blood flow was measured by an electromagnetic flowmeter, and the regional distribution of blood flow was estimated by uptake of ^{86}Rb after a bolus injection as reported previously (4).

> When partial occlusion of coronary arteries was followed by nicotine administration (Group IV), the blood pressure increased again. Under these circumstances ^{86}Rb uptake in subendocardial tissue was less than in subepicardial layers, and was markedly reduced in comparison to the normally perfused septum. This is indicative of a reduction in capillary flow to the inner portion of the myocardium as compared to septal and subepicardial flow. These changes are significant in comparison to the control and are accompanied by marked ECG changes. It appeared thus that the administration of nicotine in the presence of partial coronary artery stenosis resulted in a decrease in relative subendocardial perfusion, despite an increase in the total coronary flow. These effects may be related to the release of catecholamines (1), and similar observations have been made after the administration of norepinephrine under these circumstances (4).

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Carbon Monoxide

Studies in Man

Numerous articles have recently been published on the various effects of carbon monoxide on man and animals and are of particular interest because of the relatively high levels of carbon monoxide found in the main and sidestream smoke of cigarettes. Only those articles are discussed here which contain data on the cardiovascular effects of carbon monoxide.

Aronow and Rokaw *(3)* examined the effects of smoking-induced carboxyhemoglobin levels on angina pectoris in 10 patients with CHD. The time to the onset of angina after smoking a non-nicotine cigarette was measured. Each patient had smoked more than a pack of cigarettes a day for at least 19 years and had a classical history of exertional dyspnea. Smoking non-nicotine cigarettes failed to result in an elevation of the blood pressure or the heart rate; however, there was a significant ($P < .01$) increase in COHb levels to about 8 percent. This resulted in a significant decrease in exercise performance compared to the nonsmoking state ($P < .01$). This confirms that carbon monoxide can compromise oxygen delivery independently of the effect of nicotine.

3. ARONOW, W. S., ROKAW, S. N. Carboxyhemoglobin caused by smoking non-nicotine cigarettes. Effects in angina pectoris. Circulation 44(5): 782-788, November 1971.

Maximal oxygen consumption under conditions of carbon monoxide intoxication were studied in human volunteers by several authors *(49, 71, 72)*. COHb levels of 15 or 20 percent resulted in a proportionate reduction in maximal O_2 consumption. The volunteers responded to the decrease in oxygen-carrying capacity of the blood with a tachycardia and relative hyperventilation during moderate exercise. Carbon monoxide produces a limitation of an individual's maximal oxygen consumption by decreasing the availability of oxygen supplied under conditions of increased oxygen demand.

49. PIRNAY, F., DUJARDIN, J., DEROANNE, R., PETIT, J. M. Muscular exercise during intoxication by carbon monoxide. Journal of Applied Physiology 31(4): 573-575, October 1971.

71. VOGEL, J. A., GLESER, M. A. Effect of carbon monoxide on oxygen transport during exercise. Journal of Applied Physiology 32(2): 234-239, February 1972.

72. VOGEL, J. A., GLESER, M. A., WHEELER, R. C., WHITTEN, B. K. Carbon monoxide and physical work capacity. Archives of Environmental Health 24(3): 198-203, March 1972.

Heistad and Wheeler *(24)* reported that the hypoxia induced by carbon monoxide inhalation caused an inhibition of reflex vasoconstrictor responses despite the presence of normal arterial oxygen tension.

24. HEISTAD, D. D., WHEELER, R. C. Effect of carbon monoxide on reflex vasoconstriction in man. Journal of Applied Physiology 32(1): 7-11, January 1972.

Studies in Animals

The effects of carbon monoxide on coronary hemodynamics and left ventricular function in six unanesthetized dogs were studied by Adams, et al. *(1)*. The animals reacted to a 5 percent carboxyhemoglobin level with a 14 percent increase in coronary blood flow. Twenty percent COHb resulted in a 57 percent increase in coronary flow and slight increases in heart rate and stroke volume.

1. ADAMS, J. D., ERICKSON, H. H., STONE, H. L. The effects of carbon monoxide on coronary hemodynamics and left ventricular function in the conscious dog. IN: Proceedings of the 1st Annual Conference on Environmental Toxicology, September 9-11, 1970. Aerospace Medical Research Laboratory, Wright-Patterson Air Force Base, Ohio, AMRL-TR-70-102, December 1970. pp. 107-110.

Birnstingl, et al. *(9)* exposed young adult rabbits to 400 p.p.m. CO for periods that varied from 6 to 14 hours. The mean COHb level after a series of 22 exposures was 17 percent. A qualitative increase in platelet stickiness, as measured by the bead-column method, developed during the 24-hour period following CO exposure. The authors observed that this "...provides a possible mechanism for intimal deposition and a further link in the association between habitual smoking and peripheral vascular disease." Astrup *(5)* found the cholesterol level in the aorta of rabbits exposed to a low level of carbon monoxide for 10 weeks to be, on the average, 2.5 times higher than in the control rabbits. Both the experimental and control groups were maintained on a high cholesterol diet.

9. BIRNSTINGL, M. A., BRINSON, K., CHAKRABARTI, B. K. The effect of short-term exposure to carbon monoxide on platelet stickiness. British Journal of Surgery 58(11): 837-839, November 1971.

5. ASTRUP, P. Rökning och koronarsjükdom (11): Katheskadigende virkning af CO og hypoxi. (Smoking and coronary disease (11): Vascular damaging effect of CO and hypoxia.) Läkartidningen 67(3): 44-49, January 14, 1970.

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Smoking-Induced Carboxyhemoglobin Level. The observations of (3) Aronow and Rokaw were made on patients. However, this does not mean that healthy smokers suffer from compromising oxygen delivery. The level of carboxyhemoglobin reported was about 8% which is higher than the 5% for smokers without heart disease.

The authors have recognized the possibility that other pollutants in the cigarette smoke have not been excluded. The reduced hemodynamic response to smoking has been interpreted by the authors as due to lessened oxygen available for the myocardium. Another way of interpretation is to regard the earlier onset of angina to be a protective mechanism that is not necessarily harmful to the patient.

This technique used for detecting myocardial ischemia should be compared with that described in page 480 (a) which arrived at a different conclusion.

There are theoretical grounds for concern that other inhaled gaseous pollutants, such as oxides of nitrogen, may also act to impair the hemoglobin-oxygen transport and delivery system. Further investigation of these mechanisms is clearly indicated.

Sarnoff and coworkers[11] have found the primary hemodynamic determinant of myocardial oxygen consumption to be the total tension developed by the myocardium (heart rate times the area under the systolic portion of the aortic pressure curve). The present study shows that the product of systolic blood pressure times heart rate after exercise-induced angina was significantly less after smoking the nonnicotine cigarettes than in the nonsmoking state. This suggests strongly that less myocardial work can be performed before the onset of angina in the presence of elevated carboxyhemoglobin levels, related to lessened oxygen available for the myocardium.

Smoking high-nicotine[1-3] or low-nicotine[2,3] cigarettes causes an increase in systolic blood pressure and in heart rate, thereby increasing the myocardial oxygen demand, but this is not found after smoking of nonnicotine cigarettes.[2,3] However, smoking high-nicotine, low-nicotine, or nonnicotine cigarettes does cause elevated carboxyhemoglobin levels,[4-5] decreasing the amount of oxygen available to the myocardium. Therefore, patients with historic angina pectoris develop pain sooner after exercise following smoking either high-nicotine cigarettes,[1] low-nicotine cigarettes,[2] or nonnicotine cigarettes, in relation to at least two factors: increased myocardial oxygen demand in the presence of nicotine, and impaired oxygen delivery, whether or not nicotine is present.

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Gibbons and Mitropoulos *(20)* reported that CO inhibited cholesterol biosynthesis with accumulation of lanosterol and 24,25-dihydrolanosterol in an *in vitro* system of rat liver homogenates exposed to a 90 percent CO atmosphere. It was felt that CO may have influenced an early step in the oxidative elimination of the 14α-methyl group of lanosterol.

Smoking and Thrombosis

Previous reports of the Surgeon General on smoking and health *(62, 63, 64, 65, 66)* have reviewed the effects of smoking on thrombosis. Recent reviews and studies have not thus far yielded a unifying concept of the effect of smoking on thrombosis *(4, 18, 19, 32, 45)*.

20. GIBBONS, G. F., MITROPOULOS, K. A. Inhibition of cholesterol biosynthesis by carbon monoxide: Accumulation of lanosterol and 24,25-dihydrolanosterol. Biochemical Journal 127(1): 315-317, March 1972.

4. ARTHES, F. G. An epidemiologic survey of hospitalized cases of venous thrombosis and pulmonary embolism in young women. Milbank Memorial Fund Quarterly 50(1, Part 2): 223-243, January 1972.

18. FACCHINI, G., SEMERARO, S., DI BIASE, G., TABARRONI, F., SPAGNOLO, AUTORE, A., BONAVITA, E. Modificazioni nel soggetto anziano della reattivita al fumo di sigaretta: Ricerche sull'equilibrio emocoagulativo e fibrinolitico e sul circolo periferico. (Modifications of the reactivity to cigarette smoke in old subjects: Research on the hemocoagulative and fibrinolytic equilibrium and on the peripheral circulation.) Giornale di Gerontologia 19(10): 779-784, 1972.

19. FEINLEIB, M. Venous thrombosis in relation to cigarette smoking, physical activity, and seasonal factors. Milbank Memorial Fund Quarterly 50(1, Part 2): 123-141, January 1972.

32. KAPPERT, A. Tobacco and diabetic angiopathy. Acta Diabetologica Latina 8(Supplement 1): 429-433, September 1971.

45. ORLOVA, N. P. Some parallels between the blood coagulation activity and the condition of adrenergic and cholinergic system of the organism. Terapevticheskii Arkhiv 43: 58-62, February 1971.

CEREBROVASCULAR DISEASE

Paffenbarger and Wing *(65)* examined several precursors of nonfatal stroke in 102 patients with this disease in a population of 10,327 men who had attended Harvard University between the years of 1916 and 1940 and who also returned a self-administered questionnaire in 1966. Examination of University medical records of these former students revealed four characteristics present in youth that predisposed those individuals who were more likely to experience a nonfatal stroke in later life. These factors were: cigarette smoking, elevated blood pressure, increased weight for height, and short body stature. The age and interval-adjusted incidence rates per 1,000 were 10.1 for nonsmokers, 15.3 for smoker of 1 to 9 cigarettes, and 17.9 for smokers of 10 or more cigarettes a day. The relative morbidity ratios for the four factors cited above increased from 1.1 for patients with only one risk factor to 1.7 for those with any two risk factors, and to 3.2 for patients with any three or four risk factors.

Miyazaki *(44)* studied blood flow in the internal carotid artery using ultra sound techniques. Internal carotid blood flow was examined under a variety of experimental conditions. Inhalation of cigarette smoke in three individuals aged 27, 67, and 69 resulted in an increased blood flow due to decreased vascular resistance. This effect lasted for 10 to 20 minutes following smoking.

46. PAFFENBARGER, R. S., Jr., WING, A. L. Chronic disease in former college students. XI. Early precursors of nonfatal stroke. American Journal of Epidemiology 94(6): 524-530, December 197

44. MIYAZAKI, H. Studies on cerebral circulation by the ultrasonic Doppler technique--with special reference to clinical applicat of the technique. In: Meyer, J. S., Schade, J. P. (Editors). Progress in Brain Research, Volume 35. Cerebral Blood Flow, Amsterdam, Netherlands, Elsevier Publishing Co., 1972. pp. 1-

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Unifying Concept of Effect of Smoking on Thrombosis. The studies cited are for special groups of patients who suffer from hypercoagulability unrelated to smoking. For example, (32) Kappert made his observations on diabetics with obliterative arteriosclerosis. The results of comparison are quoted below. The Conclusion does not apply to nondiabetic patients with coronary heart disease.

> A second group consisted of ten patients with obliterative arteriosclerosis, five of whom had diabetes mellitus (average age 54 years). These cases showed diffuse stenotic obliterative changes of the arterial system of the legs with occlusion in the femoro-popliteal region on one or both sides. Before the start of the treatment they all were heavy smokers (20-40 cigarettes daily). During the test period they had given up smoking for at least two weeks. Eight out of these ten patients showed a pathological thromboplastin tolerance test which was very marked in 4 (3 of whom were diabetics). The behaviour was strictly different from the control group. An exact quantitative assessment of the increased sensitivity to smoking is not possible. But correlating to the recalcification time values of the two curves, the augmentation of the clotting tendency during smoking was 18% for the whole group. In the cases of diabetes mellitus the average increase was 27%.

SUMMARY

With the aid of the so-called thromboplastin tolerance test an increased tendency towards intravascular clotting can be demonstrated. After the discussion of the principle of this test its application in normal individuals and in patients with arterial occlusive disease is analysed. Diabetics with obliterative arteriosclerosis show an increased sensitivity to smoking which provokes a state of higher clotting tendency. This is probably one of the mechanisms through which smoking favors the development of arteriosclerosis and the acceleration of its course. In our series the diabetics with arterial occlusive disease showed the most marked reaction to the thromboplastin tolerance test after smoking.

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PERIPHERAL VASCULAR DISEASE

The association between cigarette smoking and arteriosclerosis obliterans (ASO) was investigated by Weiss *(73)*. Patients were considered to have ASO if both the dorsalis pedis and posterior tibial pulses were absent in one lower extremity and the examining physician made a diagnosis of ASO. Patients were asked the age of initiation of smoking; the daily number of cigarettes smoked; the amounts smoked at ages 30, 50, and 70; the age at which they stopped smoking; and, for males, whether they smoked cigars or a pipe. A total of 214 male cases, 206 male controls, 350 female cases, and 913 female controls were studied. The control group was composed of patients with peripheral vascular problems other than ASO but who had dorsalis pedis pulses present on initial examination. In each age and sex group, cigarette smoking was more prevalent among cases than controls. In both sexes, risks were high for smokers of less than one pack a day, and increased with the amount smoked (figures 6 and 7). It was estimated that 70 percent of nondiabetic ASO in the United States is related to the use of cigarettes. Diabetes mellitus is a major risk factor for the development of ASO; however, cigarette smoking appeared to act independently of diabetes.

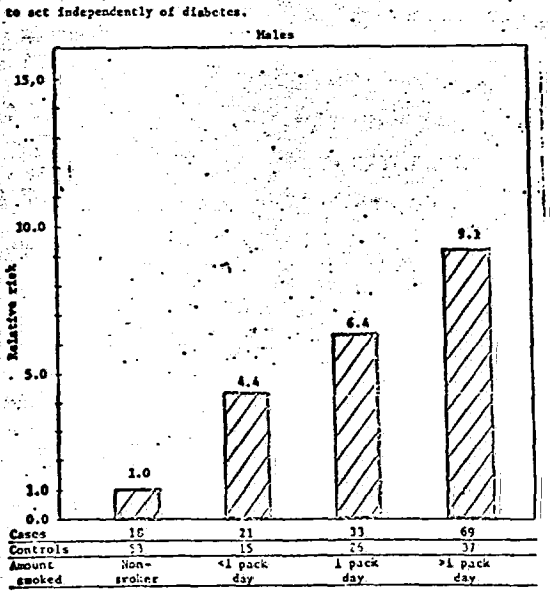

Figure 6.--Relative risk of developing arteriosclerosis obliterans (ASO) for males by amount of cigarettes smoked.

SOURCE: Weiss, N. S. *(73)*.

WEISS, N. S. Cigarette smoking and arteriosclerosis obliterans: An epidemiologic approach. American Journal of Epidemiology, 95(1): 17-25, January 1972.

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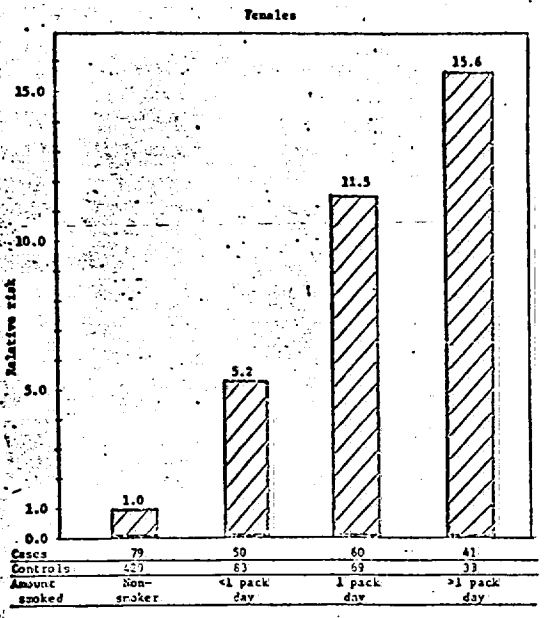

Figure 7.--Relative risk of developing arteriosclerosis obliterans (ASO) for females by amount of cigarettes smoked.

SOURCE: Weiss, N. S. *(73)*.

Preuss, et al. *(50)* examined the relationship between several factors including cigarette smoking, blood pressure, weight, and history of diabetes and the development of occlusive disease of the peripheral arteries in a population of 300 patients in Germany. Group I consisted of 150 patients with a mean age of 59 years who had intermittent claudication. Most of these patients were ambulatory. The 150 patients in Group II had a mean age of 60 years and had far advanced peripheral arteriosclerosis with ischemic pain at rest or evidence of gangrene. There was no control group of patients free of vascular disease. There were few nonsmokers in either group of patients, but the group with the more severe disease had a higher average daily consumption of cigarettes than did Group I.

PREUSS, E.-G., EDER, R., WELLER, F. Risikofaktoren bei peripheren arteriellen Verschlusskrankheiten unterschiedlichen Schweregrad. (Risk factors in occlusive diseases of the peripheral arteries, of varying severity.) Zeitschrift für die gesante innere Medizin und Ihre Grenzgebiete 25(10): 464-468, May 15, 1970.

The influence of cigarette smoking on late occlusion of aorto-femoral bypass grafts was examined by Wray, et al. *(75)*. A series of 100 patients who had aortic reconstruction for aneurysmal or aortoiliac occlusive disease between 1965 and 1968 were studied. Of the patients who had bypass grafts for occlusive disease, 30 patients smoked cigarettes and 16 did not. Late occlusions from thrombosis occurred in 9 patients, each of whom was smoking more than a pack of cigarettes a day at the time the thrombosis occurred ($P < .5$). The authors recommend cessation of cigarette smoking to all patients undergoing vascular reconstruction.

75. WRAY, R., DePALMA, R. G., MURAY, C. H. Late occlusion of aorto-femoral bypass grafts: Influence of cigarette smoking. Surgery 70(6): 969-973, December 1971.

Schnauss and Arlt *(55)*, Wilbert *(74)*, and Kradjian, et al. *(39)* reported a greater than 93 percent prevalence of cigarette smoking in three separate series of patients with severe peripheral vascular disease.

55. SCHNAUSS, A. K., ARLT, E. Morphologische Befunde, postoperative Komplikationen, Letalität und Liegedauer nach Amputation wegen Durchblutungsstörungen. (Morphological findings, postoperative complications, mortality and duration of bed rest following amputations occasioned by disorders of the peripheral circulation. Zeitschrift fur Ärztliche Fortbildung 64(2): 84-87, January 15, 1

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Isacsson *(23)* performed venous occlusion plethysmography in 684 men aged 55 in Malmö, Sweden. In addition to a detailed smoking history, a number of other factors were studied, including blood pressure, pulse, height, weight, ECG, heart volume, and blood lipids. The plethysmograms were taken on both legs simultaneously with the patient in the recumbent position. Measurements were taken at rest and during reactive hyperemia produced by obstructing arterial inflow to the legs for three minutes with a blood pressure cuff applied to the thigh. Smokers had a significantly lower mean flow capacity (MFC) than did nonsmokers. The MFC in the legs was reduced in direct proportion to the amount of tobacco consumed per day regardless of the mode of smoking. The MFC was significantly lower with inhalation ($P < .001$) and with increasing amount smoked ($P < .001$).

Matsubara and Sano *(42)* studied the effect of cigarette smoking on human precapillary sphincters of the leg using a pressure plethysmograph applied to the calf. Precapillary sphincter tone was estimated using the capillary filtration coefficient, which is the product of "functional capillary service area" and the filtration constant of the capillary wall. Four healthy male subjects were tested. All were regular smokers of cigarettes who had not smoked for the previous 24 hours. When cigarette smoke was inhaled deeply at 30-second intervals over a 12- to 15-minute period, there was a 19 percent decrease in the capillary filtration coefficient, indicating closure of precapillary sphincters. Cigarette smoking also resulted in a 31 percent decrease in calf blood flow, indicating some degree of constriction of the arterioles in the leg. The pressure volume curves of the venous system were not affected by cigarette smoking.

Halstad and Wheeler *(24)* examined the effect of carbon monoxide on vascular resistance and reflex vasoconstriction in the forearms of 12 healthy men 19 to 23 years old. After control measurements were taken, the subjects were exposed to enough carbon monoxide to produce carboxyhemoglobin levels of 18 to 20 percent or 25 percent. Carbon monoxide did not cause a change in alveolar PO_2 or PCO_2. The arterial oxygen saturation was less than 75 percent, but this decrease did not result in altered resting arterial pressure nor was there much evidence of sympathetic stimulation. Carbon monoxide hypoxia did result in a significant decrease in vascular resistance in the resting forearm ($P < .05$). Carbon monoxide exposure also resulted in a significant depression of the vasoconstrictor responses of the forearm following the application of negative pressure to the lower body ($P < .001$) and of ice on the forehead. It appears that the hypoxia induced by carbon monoxide causes an inhibition of reflex of vasoconstrictor responses despite the presence of normal arterial oxygen tension.

42. MILBERT, L. Nikotinkonsum und arterielle Verschlusskrankheit. (Nicotine consumption and arterial occlusive disease.) Medizinische Klinik 66(35): 1190-1192, September 3, 1971.

39. KRADJIAN, R., BOWLES, L. T., EDWARDS, W. S. Peripheral arterial disease in Ceylon. Surgery 69(4): 523-525, April 1971.

29. ISACSSON, S.-O. Venous occlusion plethysmography in 55-year old men. A population study in Malmö, Sweden. Acta Medica Scandinavica (Supplement 537): 1972. 62 pp.

42. MATSUBARA, I., SANO, T. Effect of cigarette smoking on human precapillary sphincters. British Journal of Pharmacology 45(1): 13-20, May 1972.

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Source: https://www.industrydocuments.ucsf.edu/docs/mfk0000

SUMMARY OF RECENT CARDIOVASCULAR FINDINGS

In addition to the summary presented in the introduction to this chapter based on previous reports of the health consequences of smoking, the following statements are made to emphasize the recent developments in the field:

1. Recently conducted epidemiological studies from several countries continue to confirm that cigarette smoking is one of the major risk factors contributing to the development of coronary heart disease.
2. Epidemiological evidence suggests that black men in the rural South respond to the same risk factors for coronary heart disease, including cigarette smoking, as white men do but apparently at lower disease rates, which appears to be in part due to differences in physical activity.
3. Data from several epidemiological and experimental studies suggest that cigarette smoking is a major risk factor in the development of peripheral vascular disease. This may in part be due to the decreased blood flow in arterioles and capillaries associated with cigarette smoking. Smoking may complicate the surgical intervention in this disease by contributing to late occlusion of the treated vessel.
4. A laboratory test has been developed which accurately measures nicotine levels in blood. This test will be useful in understanding nicotine metabolism and can be used as an objective measure of cigarette smoke inhalation.

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Summary of Experimental Studies. The recent experimental work does not support the contention that smoking decreases blood flow in arterioles and capillaries. At least two types of evidence were mentioned: page 479 on electrocardiogram and page 480 on lactate extraction performed on healthy smokers and on patients with coronary heart disease who were also smoking cigarettes. The positive results appearing on page 483 were on smoking of nonnicotine cigarettes and on page 482 related to nicotine in animal heart. The conclusion in the document should state that recent evidence does not show that cigarette smoking decreases flow.

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XV. RECOMMENDATIONS TO THE COUNCIL FOR TOBACCO RESEARCH

There are two areas of investigation which it is important to elucidate further: the relationships between cigarette smoking and coronary heart disease. They are as follows:

A. Prospective studies of patients with angina pectoris or myocardial infarction. The primary aim of the investigation will be to identify patients with tobacco angina. This group will be compared with patients having effort angina with no previous history of infarction, postinfarction patients, and matched controls. The following will be examined: (1) smoking habits, (2) acute effects of cigarette smoking on carboxyhemoglobin, blood lipids and coagulability of the blood; (3) oxygen consumption and electrocardiogram at various levels of exercise; (4) determination of risk factors and the outcome of reducing one at a time; and (5) prognosis and development of complications. The list has been selected on the basis of the present state of knowledge derived from the considerable amount of information obtained from epidemiologic investigations.

B. Chronic effects of cigarette smoke in animals. A model that will allow measurement of cardiac function and detection of myocardial ischemia is necessary. In addition to the antemortem and postmortem examination of the heart, the following will be measured: carboxyhemoglobin level, extent of absorption of nicotine, coagulability of the blood, concentration of lipids in the blood, catecholamine excretio glucose tolerance and insulin assay. With the use of suitable animals exposed to cigarette smoke and of controls, one can obtain an answer to the question as to whether or not cigarette smoking causes coronary heart disease.

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